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Tribute

A Tribute to Dr Faisal Masud:

Ayesha Najib
MD FAAP, USA

"As is a Tale, so is Life: Not How Long it is, but how good it is, is what Matters"
Seneca

It was a cold January morning in 1990, dressed in a bright new white coat I was a newly minted house officer in North Medical Ward. It was the second day of my work life, I had a new case to present. I started nervously gaze down, narrated my patient's history in breathtaking speed and looked up tentatively, standing diagonal to me listening intently was a lean man with piercing eyes. He looked at me and gave me a gentle nudge, "Putter, your history is never complete without pertinent negatives,' and this simple but profound lesson lasted me a lifetime.

He was a gifted diagnostician, not by accident- he arrived at his diagnosis with a meticulous history and a physical exam worthy of art. The fact that he diagnosed a drug reaction based on history during Punjab Institute of Cardiology (PIC) incident of 2011 is the best testimony to his diagnostic skills. One of his many gifts was reading body language, he often knew what was on a patient's mind before he/she uttered a single word was. He always started with reassurance, "Baba jee tuse changay ho jayo gay." Like Hippocrates, he never forgot to comfort his patients.

Over a span of thirty years, I got to know Dr Faisal in many roles, as a phenomenal teacher, a master clinician, an extraordinary leader, a great human being and most of all a friend. I first met Faisal Saab (as we affectionately referred to him) in 1988, when he delivered a lecture on Diabetic Ketoacidosis (DKA) at Patiala block in his signature concoction of English, Urdu and Punjabi. A wiry man with salt and pepper hair, who left us speechless with his command of subject and captivating teaching style, and thus started a journey of life time of respect and adulation for me.

In 2014, as president of KEMCAANA, I asked him what we could do for KEMU, and his answer was: "The job of a university is to produce original knowledge. I need your help to develop original research at KEMU." He firmly believed that the biggest asset of a country was not its riches, oil or gold, but original knowledge. One of his brilliant former students, Dr Rehan Qayyum volunteered and successful taught a faculty research mentorship program for faculty, which led to international research publications from KEMU faculty. Following year, when we met him, he smiled. Research publications from KEMU always made him happy. I earned enough respect that every December, he would give me the honor of having lunch with him at Café Ayanto,

Dr Faisal firmly believed that a strong faculty was the biggest asset of KEMU. He took a personal interest in hiring and developing young faculty. A connoisseur of literature, poetry, philosophy, art, opera and music, he wanted to inculcate flair in his faculty members. He often discussed books, movies and music during young faculty seminars. He was a lifelong learner, who even took Punjabi lessons formally from a Punjabi professor, to communicate better with his patients. An almost le cordon bleu trained chef, it was amusing to watch him give instructions to his chef from his VC desk on how to bake a fruit cake or whip up a café late.

Faisal Sb had a keen eye for architecture and touring Patiala Block through his eyes was a special treat. I had no idea that library hall dimensions were that of Da Vinci's Vitruvian Man, he proudly showed us the stunning renovated library hall. Each and every door knob, window fixture, light shade had been painstakingly reproduced. It had never looked better. He brought it back to the glory which I had never witnessed before. Each and every slab of marble in library hall bears a testimony to his eye, he would stop construction till the exact grain of Ziarat marble arrived to ensure continuity.

One only has to visit Diabetes Metabolic Center (DMC) at Services Institute of Medical Sciences to get acquainted with his vision posthumously. A comprehensive diabetic center, first of its kind in public center established with his family's donation where all services are provided under one roof. From the electronic medical records (a software he created), token system, diabetic educators and dieticians to bariatric weighing scales, no details were

spared!

Dr Faisal was an original. A man of character and integrity who lived an extraordinary life.

With his piercing gaze, and snowy mane, he had a presence and charisma that demanded attention. Perhaps it came from who he was inside, pure as the driven snow. He achieved in 65 years, what most of us couldn't do in 165 years. He taught scores of students, trained young physicians, created and led institutions, mentored faculty, led Dengue Expert Advisory Group and campaign with phenomenal success, advised government officials on preventive health, health policy matters and much more. He never cut corners, he lived a life where the end did not justify means. He set an example with his life, where he made you want to be a better person. He was a patriotic citizen that gave back to his country, fully and freely without any expectations. Acclaim was never the point of service for him.

Dr Faisal has left a huge void in our lives. He has taught us the meaning of true service, to his family, friends, patients and most of all his country. He lives on all of us whose lives he so profundly touched. We felt his presence and will continue to do so as long as we live. And isn't that the whole point of our time on earth? What an example he set for us.

I did not want to write this. Perhaps, I did not want to acknowledge the finality of this moment that he is truly gone. Gone but not forgotten, for he touched countless lives, left this world a much better place than he found it. He was never afraid of death, he didn't want to linger and even in death he got what he wanted. He departed on his own terms, suddenly one day when we least expected it, left us wishing even in death that we could leave like him.

Blog

Edward Morris
MD PRCOG

As President of the Royal College of Obstetricians and Gynaecologists, I am proud to lead a truly global organisation. We may have our headquarters in London, but our activity and influence reaches far beyond the UK, with Members and Fellows around the world working tirelessly to improve healthcare for women and girls everywhere.

Wherever we are in the world, it is a busy period for the whole of our specialty. The pandemic has touched us all. Obstetrics has not stopped, yet it has been much harder to deliver a safe service during the pandemic and especially while trying to restore other services. The pressures on gynaecology, especially for those managing and prioritising waiting lists, are also significant. This is something I have observed in my own unit, here in the UK, but I know that these are challenges faced by doctors and other healthcare professionals throughout the world.

In mid-June this year we hosted our first entirely digital RCOG World Congress. Over 3000 delegates attended from more than 85 countries, enjoying 240 sessions over 4 days from their homes and places of work. As always, one of the main highlights was the annual meeting of our International Representative Committee and international Liaison Group Chairs. The shared achievements, commitment and resilience demonstrated by the global O&G community cannot be underestimated, in what has been a truly unprecedented 12 months for us all.

The fact that Congress attracts such a diverse group of delegates from all over the world really shows the global nature of the College, and this is something I am keen to develop further. Our Centre for Women's Global Health works to achieve our goal of improving women and girls' lives, through the delivery of respectful, high quality and accessible health care all over the world. The RCOG's new five year strategy has further strengthened this mission.

One of our priority areas is the advancement of gynaecological health. Gynaecology is a neglected area of global health. Many gynaecological conditions are highly stigmatised and surrounded by secrecy, including sexually transmitted infections, fistula and infertility. Given this stigma and secrecy, it is perhaps not surprising that gynaecological conditions cause more mortality and morbidity than many of the other global health focus issues including malaria, HIV/AIDS and TB. This is particularly the case in countries where resources are scarcer.

The RCOG is committed to helping eliminate the suffering of women and girls from preventable gynaecological conditions. We have developed a unique training programme focused on essential skills for multi-disciplinary health professionals working in low-resource contexts to support them in the delivery of high-quality, respectful gynaecological care. The training has been designed to work effectively where resources are limited, ensuring it delivers value for money for the health system.

The training encompasses several gynaecological topics, including cervical cancer, contraception, abnormal uterine bleeding, infertility and fistula and focuses on basic skills to identify symptoms and treat women earlier.

Another priority area for the College is the promotion of safe abortion and post abortion care, to the extent permitted within the law. An estimated 25 million unsafe abortions occur every year, making it one of the leading causes of maternal mortality and morbidity worldwide. However, abortion related deaths are largely preventable by providing access to contraception, safe abortion care (performed in line with clinical best practice), and timely post-abortion care. Through our Making Abortion Safe programme, we are working with healthcare professionals to expand access to safe abortion care for all women and girls who need it.

To ensure the O&G community can continue to improve the health of women and girls around the world, we have joined with partner organisations to speak out about recent cuts to UK overseas aid spending from 0.7% of Gross National Income to 0.5%.

In a letter to the Prime Minister we warn that cutting the resources that the UK provides to lower and middle-income countries will cause irreversible harm to the health and wellbeing of women, girls and their families. We know that these cuts will disproportionately impact women and girls and that the lost funding would have helped prevent around

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250,000 maternal and child deaths.

The pandemic has shown that we all have a shared interest in improving public health across the globe, so we will continue to call on the Government to reverse these damaging cuts and reaffirm its commitment to improving access to quality healthcare for women and girls around the world.

Improving the health of women and girls, wherever they are, no matter their circumstances, is at the heart of everything we do at the RCOG. We have made great progress through training and education, speaking out on key issues and working with our extensive network of Members, Fellows and partners – locally, nationally and internationally - but there is always more to do. We will continue to strive towards our ultimate goal of improving women's health and the clinical practice of obstetrics and gynaecology in the UK and across the world.

Esculapio - Journal of Services Institute of Medical Sciences

Guest Editorial

Addressing the Global Pandemic of Violence Against Women

Shehla Baqai

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Background

Violence against women and girls (VAW&G) is a grave violation of fundamental human rights.[1] It is a major global, public health issue that violates autonomy and hinders development. VAW&G is now a global pandemic being endemic in every country, culture and social strata; causing deliberate harm to millions of women and their families.[1] VAW&G is devastatingly pervasive and starts at an alarmingly young age with reports of sexual abuse of girls as young as six months.[1,2] At times may start in utero with female feticide. VAW&G can take many forms –from domestic violence to trafficking, sexual abuse to child marriage, genital mutilation to femicide. The perpetrator usually is someone closely known to the family. Violence not only affects women's physical, mental, sexual, and reproductive health adversely, but also has negative impact on family, society and country. VAW has tremendous financial impact, due to greater health care and legal expenses, reduced productivity; resulting in lesser national budget and overall development of the nation.[3]

Magnitude of the problem

According to World Health Organization (WHO) estimates, globally 1 in 3 (30%) women in their lifetime are subjected to physical or sexual violence.[2] These statistics have remained unchanged for the last decade. The most affected are from Low and middle income countries (LMIC).[2]

COVID-19 pandemic has accelerated women's exposure to violence, as a result of lockdowns, more time at home with abusers, rising stress, limited access to health facilities and disruptions to vital support services. Domestic violence has emerged as a shadow pandemic showing a massive global rise during COVID-19 lockdown [4.5].
Unlike COVID-19, we don't have a vaccine for violence against women!

Situation in Pakistan

Cases of gender-based violence (GBV) and VAW are grossly under reported in Pakistan. Thousands of women who face violence remain missing from the statistics. The crime is never reported because the offender is usually from the family; it becomes an issue of honor. Everyday social media and news print reports 2 to 3 cases of VAW. According to estimates in November 2020 by White Ribbon Alliance, 60 to 70 percent of women in Pakistan face violence and abuse at some stage of their life. Around 5,000 women are killed every year while thousands become disabled because of domestic violence. Pakistan has witnessed several cases of GBV in the past few months highlighting the enormity of the problem. Problem of VAW in Pakistan is growing and has assumed epidemic proportions, impossible to ignore.In Pakistan violence against women (VAW) is both a crime and a socially accepted norm. Despite minimal improvements in gender-specific legislation in Pakistan, violence against women hasn't declined in fact it's on the rise. Patriarchal Culture, poor parenting, lack of basic life skills, little or no respect for women and weak implementation of laws promote VAW. While there is widespread rhetoric about the pivotal role of women in the development of a nation; laws aiming to protect women; separate ministries for women development; but when it comes to effectively protecting women against violence rooted in patriarchy, the same authorities are either apathetic, complicit or drag the court proceedings to an extent that it becomes redundant.

Pakistan has several laws and policies against various forms of violence. Implementation of the policy remains a challenge. Women are denied the basic right to education, inheritance and choosing their life partner. Most of acid throwing incidents take place as

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a revenge of refusal to marriage proposal or illicit relationship, leaving the women scarred forever.[6] Many women lack access to free or affordable essential services in health, police, justice and social support so as to ensure their safety.[7] In Pakistan the triangular alliance between patriarchy, ignorance and illiteracy has prevented any meaningful rights-based strategy to address VAW&G.

Solutions

25th November is the International day for elimination for VAW is nearing and we are far from the goal. Reported gender equality indicators, are abysmal and suggest we won't be able to achieve SDG target to end VAW. System has failed to deliver justice to the abused, opening the path for more abuse incidents. We need to accelerate our actions. Short-term, quick-fix solutions, suo moto actions, politicians and rights activists' verbal solidarity with the victims and condemnations will never prevent recurrence of the incidents. Using the human rights based approach, deep rooted sustained efforts are required by the policy makers, government, society, communities, health sector, judiciary and individuals to promote a societal attitudinal change, fostering respect for women and improved access to medical and social services to women.[7,8]

Following areas need to be strengthened.

1.Policy and Laws- There needs to be stronger leadership and political will to develop, review, institute and implement policies, strategies, laws and regulations that address to end violence against women and promote gender equality (equitable access to education, pay, property/ inheritance rights). Government should invest in capacity building of all service providers (health, judiciary and education). VAW survivor help facilities to be established in health care facilities and included in essential services in times of disaster and crisis. Introduce easily accessible user friendly Women Safety Phone Apps and help lines. Adopt measures to end poverty; promote education andempower women, make women aware of their right to access quality health services State must enforce its laws with accountability. Judicial and police officers who are negligent in their duties towards preventing VAW should be held accountable.

2. Data Collection: Solutions require an acknowledgement of the problem, and openness to discovering uncomfortable truths about ourselves and others. There is a dire need to strengthen data collection, reporting and documentation for records. Investing in high-quality surveys on VAW will help determine prevalence and cause paving the way for elimination of VAW.

3. Health Sector - The health care prrofessionals (HCPs) have the unique opportunity of being the first ones with whom the victims come in contact. Health sector plays a pivotal role in the care of VAW survivors, by providing comprehensive health care to women subjected to violence and as an entry point for identification of the need to refer women to other support services such as shelter, legal and social support they may need.[9] There is a need to train and strengthen the capacity of HCP to identify, examine, offer first line support and medical treatment to survivors of VAW, identify survivor needs, establish referral linkages and respond in a caring and sensitive way.

VAW needs to be included in the curricula of all health care providers-in under graduate training as well as specialist training of obstetrician gynecologists and in continuing education programs for all HCPs.[9]

4.Society: Communities and society have an important role in transforming attitudes, beliefs, and norms to respect women, end VAW&G. As a whole, we need to promote education, respectful relationships and awareness about their rights. Boys need to be reared to respect women and children. The victims need to be taught that violence is intolerable and must be reported. Respect for women to be inculcated from the beginning in homes, communities, work-place and society at large. Discourage attitudes that discriminate against women and girls, especially regarding the acceptability of violence against women, through school- and community based programs and interventions.[9,10] Art of parenting needs to be addressed.[11] Support and scale up national programs and strategies for prevention. Strengthen prosecution and documentation.[7,9,10,11]

Violence against women and girls cannot be justified and must stop.[10] Reflecting on the injustices meted out to women, the state should demonstrate its responsibility by not just punishing the perpetrators but develop strategies to reform the system. Let's all become agents of change and nurture a society which promotes gender equality, respectful relationships, equitable & inclusive communities, work places and institutions. **Remember "Violence against women & girls is preventable."**

We can turn the tide, change the narrative and create societies where VAW is unthinkable.

Conflict of Interest None

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The Effect of Nutritional Intake on Weight Change in Tuberculosis Patients Undergoing Antituberculous Therapy

Shabbar Hussain Changazi,[1] Usman Ali Rahman,[2] Syed Muhammad Bilal,[3] Samiullah Bhatti,[4] Zahid Iqbal,[5] Qamar Ashfaq Ahmed[6]

Abstract

Objectives: To determine the effect of nutritional intake on weight change in tuberculosis patients undergoing anti tuberculosis treatment.

Methods: It was a cross sectional study conducted at Pulmonology Department, Gulab Devi Hospital Lahore. Both male and female patients "with" age 10 years and above suffering from tuberculosis were included in the study. The weight of the patient at the start of the treatment was obtained and followed for six month. Demographic information of patient (name, age, sex, address) was obtained and frequency of weight change was recorded. Nutritional intake of patients was monitored through food frequency questionnaire. All the data was entered on a predesigned questionnaire. Data was entered, cleaned and analyzed using SPSS version 24.0.

Results: In this study 224 patients were included with mean age of 35.06 ± 17.6 years (range 10 to 80 years). One hundred and thirty-two (58.9%) were males while 92 (41.1%) were females. One hundred and forty six (65.2%) were married while 78 (34.8%) were unmarried. Mean weight change in all 224 patients was 2.95 ± 3.11 kg. It was observed that patients taking legumes, rice, sugar and apple in diet had weight gain with statistically significant difference. It was further observed that greater mean intake of oranges, tomatoes, lemons and spinach was associated with no weight gain with statistically significant difference.

Conclusion: In conclusion, certain food types (legumes, rice, sugar and apple) when used in conjunction with chemotherapy for tuberculosis treatment helps gain weight and leads to better treatment outcome.

Keywords: Nutritional Intake, Weight gain, Weight loss

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Introduction

Tuberculosis remains the leading cause of death due to a single infectious agent and one of the top 10 causes of death worldwide. According to WHO statistics 10 million people contracted the disease and 1.5 million people died in 2018 due to this deadly disease.[1] Majority of this disease burden is concentrated in the South East Asia and Africa. These two regions are home to some of the world's most poor nations. Most of these countries are classified as low or lower-middle income economy group. Low socioeconomic status has direct association with disease incidence and mortality due to overcrowding, unhygienic living conditions, malnutrition and poor access to healthcare.[2] Nutritional support is an important adjuvant therapy during treatment of Tuberculosis with anti-tuberculous therapy.[3]

Adequate provision of nutrition with counseling helps overcome macro and micronutrient deficiency observed at the diagnosis of Tuberculosis.[4] With a balanced diet, reduced breakdown of protein into amino switch the catabolic state into net buildup of body protein.[5] High Cholesterol content food may lead to speedy clearance of Mycobacterium from body. Sputum culture turns negative faster in patients fed with cholesterol rich diet.[6] Vitamin and mineral deficiency during tuberculosis is better managed with combination of supplements and chemotherapy as compared to chemotherapy alone. Food containing these micronutrients assists in overcoming the secondary immunodeficiency due to

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lack of these essential diet components.[4]

Good diet significantly improves body composition and physical functioning in well fed patients. Appreciable increase in body weight, total lean mass, total body fat and significant improvement in grip strength is observed in well fed people.[7] Nutritional support and subsequent weight gain significantly reduce the risk of unsuccessful treatment outcomes as compared to population with poor nutritional support.[4] The useful impact of nutritional support is observed when started early in the disease process. Late intervention with god diet fails to show any beneficial outcomes.[7] Individual patient's response to nutritional support is unpredictable. Time required to normalize nutritional deficiency and to gain sizeable weight is undefined and may vary among different patients.

Good nutritional intake have a direct impact on weight change and thus treatment outcome of patients on anti tuberculosis therapy. According to Sameul B et al treatment failure was less in patients having better nutritional intake as compared to poor nutritional intake. Treatment failure was present in 84 (21%) patients who had poor nutritional intake as compared to 15 (09%) which received good nutritional intake.[8] Similarly according to Bernabe-Ortiz A et al successful treatment was seen in the patients who gained 1 Kg during the first month of treatment, while the patient who lost weight during the first month had treatment failure. By the end of the fourth month, the former group gained an additional 2kg and only 0.2 Kg weight gain was noted in the treatment failure group.[9]

Aim of our study was to identify effect of nutritional intake on weight change of patients undergoing anti tuberculosis treatment and also determine individual contribution of these food types on weight gain in local set up.

Methods

It was a cross sectional study conducted at Pulmonology Department, Gulab Devi Hospital Lahore from July, 2018 to June, 2020. After approval from institutional review board patients with diagnosis of tuberculosis (pulmonary and extra pulmonary) were followed up to the completion of treatment (6 months). Non-probability convenience sampling technique was used. Both male and female patients with age 10 years and above suffering from tuberculosis were included in the study. Patients having co morbidities like diabetes, chronic liver failure, chronic renal failure and those operated for abdominal surgery as a result of tuberculosis were excluded from the study as they can interfere in weight change of the patient. The weight of the patient at the start of the treatment was obtained and followed for six month. Demographic information of patient (name, age, sex, address) was obtained and frequency of weight change was recorded. Nutritional intake of one week of 224 patients included in this study was documented on food frequency questionnaire on every visit. Drug compliance was also monitored. Patients were followed fortnight for 2 months and then monthly for next four months. All the data was entered on a predesigned questionnaire. Data was entered, cleaned and analyzed using SPSS version 24.0. Frequency tables were generated for all possible variables. Means and other parameters of central tendency were calculated for continuous data. Chi Square was applied to find out association between categorical variables. Means were compared using student's t test or ANOVA where applicable. A sample size of 224 was calculated using confidence interval of 85%, margin of error of 5% and population proportion of 50%.

Results

In this study 224 patients were included with mean age of 35.06 ± 17.6 years (range 10 to 80 years). One hundred and thirty two (58.9%) were males while 92 (41.1%) were females. One hundred and forty six (65.2%) were married while 78 (34.8%) were unmarried. Shapiro-Wilk test was done to check the normality of the data. The test showed normal distribution of population.

Mean weight change in all 224 patients was 2.95 ± 3.11kg. Mean weight gain was recorded in 175 (78.1%) patients and 21 (9.37%) patients had no change in weight. Mean weight loss was seen in 28(12.5%) patients. Mean height of patients included in this study was 5.3 ± 0.44 feet (range 3.4 to 6.2 feet). One hundred and sixty nine (169) (75.4%) had pulmonary tuberculosis while extra pulmonary tuberculosis was found in 55 (24.6%). Out of these extra pulmonary tuberculosis, tuberculous lymphadenitis was most common, 21 (38.2%) followed by pleural 20 (36.32%). Two hundred and twenty (220) (98.2%) patients were cured from tuberculosis while 2(0.89%) had treatment failure and 2 (0.89%) were transferred to MDR program. Drug compliance was seen in 217 (96.8%) patients while 7 (3.12%) patients had no drug compliance.

It was observed that patients taking legumes, rice, sugar and apple in diet had weight gain which was statistically significant. (Table 1)

Discussion

Tuberculosis is a chronic inflammatory disease associated with weight loss and low BMI at the time of diagnosis despite intake of high calorie diet.[10] A well-proportioned high calorie diet in combination with ATT gradually improves the body weight during the course of treatment.[11,12,13] Our study showed the same trend with 175 (78.1%) patients showing body weight gain at 6 month of treatment follow up. Mean weight change recorded in all 224 was 2.95±3.11 Kg. Weight loss was recorded in 28(12.5%) patients with 21(9.37%) showing no changes in weight. A study conducted by Sanchez et.al in Los Angeles on 24 tuberculosis patients recorded an increase in 3.02 ± 0.81 kg (5.5%) of body weight by 4 weeks and by 8.59 ± 0.97 kg (15.6) at 24 weeks of follow up.[12]

Result showed recovery of 220 (98.2 %) from the tuberculosis at the end of the treatment. Higher weight gain was seen in patients who were diseases free as compared to at the 6 months of follow up. Antonio Bernabe-Ortiz et.al noted a positive correlation between

Table 1: *Association of Consumption of Various Food Types with Weight Gain Using Chi Square Test*

Variable	Weight Gained		Weight Not Gained		Total N (%)	p value	Remarks
	N	%	N	%			
Egg							Not
Yes	144	79.1	38	20.9	182(81.3)	0.453	Significant
No	31	73.8	11	26.2	62(27.7)		
Milk							Not
Yes	130	78.3	36	21.7	166(74.1)	0.90	Significant
No	45	77.6	13	22.4	58(25.9)		
Yogurt							Not
Yes	100	75.2	33	24.8	133(59.4)	0.199	Significant
No	75	82.4	16	17.6	91(40.6)		
Fish							
Yes	31	83.8	6	16.2	37(16.5)	0.362	Not Significant
No	144	77	43	23	187(83.5)		
Chicken							
Yes	130	77.8	37	22.2	167(74.5)	0.90	Not Significant
No	44	78.6	12	21.4	57(25.5)		
Mutton							
Yes	139	79.9	35	20.1	174(77.7)	0.207	Not Significant
No	35	71.4	14	28.6			
Beef							
Yes	140	80	35	20	175(78.1)	0.200	Not Significant
No	35	71.4	14	28.6	49(21.9)		
Legumes							Significant
Yes	162	80.6	39	19.4	201(89.7)	0.008	
No	13	56.5	10	43.5	23(10.3)		
Chapatti							
Yes	173	78.3	48	21.7	221(98.7)	0.525	Not Significant
No	2	66.7	1	33.3	3(1.3)		
Rice							Significant
Yes	169	79.7	43	20.3	212(98.7)	0.015	
No	6	50	6	50	12(5.4)		
Apple							
Yes	171	79.5	44	20.5	215(96)	0.026	Significant
No	4	44.4	5	55.6	9(4)		
Sugar							
Yes	164	80.8	39	19.2	203(90.6)	0.003	Significant
No	11	52.4	10	47.6	2.1(4.4)		

weight gain and disease outcome. Patients with good outcome gained 1 kg on average by the end of the first month of treatment and additional 2 kg gain was seen at the 4 months of follow up. Tuberculous patient with poor outcome lost 1 kg at the end of first month[11]. A systemic review and meta-analysis reported rapid negative conversion rate of sputum smear and culture in nutritional support group compared to control group.[14]

Our study is distinctive for showing significance of various food types in improving BMI during tuberculosis treatment. Contribution of individual food type, vegetables and fruit has been rarely studied in past. Nutritional assessment was done using food frequency questionnaire which is a standard procedure. In protein intake only legumes had statistically significant association with weight gain of the patient. Patients using legumes in their diet had more weight gain as compared to patients not using legumes. Consumption of other protein containing diet like eggs, milk, yogurt, chicken, mutton and beef had no statistically significant association with weight gain.

In carbohydrates, sugar and rice intake had association with weight gain of the patient. Other diets including chapatti, candy, chocolates and bread had no association with weight gain of the patient. We also found that no association was present between fat diet and weight gain of the patients. Among fruits apple had a positive association with weight gain of the patients. Other fruits like banana, orange, guava and lemon had no significant association with weight gain of the patient. Among vegetables no association was found.

A multicenter study with large sample size can be done to more accurately link affiliation of diet with weight gain and treatment outcome. Number of calories consumed daily was not determined during assessment of patients. This limitation restricted us to show any correlation between the amounts of calories consumed daily and weight gain. The type of mass acquired during the weight gain was not determined due to lack of resources and study limitations. Contribution by fat and protein mass towards weight gain is a separate topic and needs dedicated study.

Conclusion

In conclusion, diet when used in conjunction with chemotherapy for tuberculosis treatment helps gain weight and leads to better treatment outcome. Not every type of food consumed daily contributes towards weight gain. Certain type of food, vegetable and fruit have significant role in weight gain while other food don't contribute in gaining weight during tuberculosis treatment.

Conflict of Interest: None

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Authors Contribution

A U: Conceptualization of Project,
B S: Data Collection
I Z: Literature Search
H S: Statistical Analysis
B M S: Drafting, Revision
A A Q: Writing of Manuscript

Comparison of the Frequency of Relapse After Treatement of Acute Exacerbation of Asthma with Oral Dexamethsone Versus Oral Prednisolone in Children

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Abstract

Objective: To compare the frequency of relapse after treatment of acute exacerbation of asthma with oral dexamethasone versus oral prednisolone in children aged 2-12 years.

Methods: Total 400 patients as per the inclusion criteria were enrolled. The cases were divided into 2 clusters with equal number of participants. 200 participants were in oral dexamethasone group and 200 in oral prednisolone group. After standard treatment of acute asthmatic exacerbation (nebulization with salbutamol) in emergency department, group 1 was given 0.6mg/kg of tablet dexamethasone in emergency continued for next 2 days and placebo agent for next 3 days, group II was given tablet prednisolone (2mg/kg) in emergency and 1mg/kg/day dose for next 5 days.

Results: Children 2 to 12 years of age were included in both groups, with mean age of 5.55±2.33 years in dexamethasone group while 7.57±2.37 years in prednisolone group. Duration of improvement of symptoms was 2.00±0.21 days in dexamethasone group while 2.00±0.48 days in prednisolone group. Relapse was seen in 18% in dexamethasone group as compare to 15% in prednisolone Group, difference in relapse rate was not significant in both groups(p=0.419).

Conclusion: Two days course of oral dexamethasone has almost similar frequency of relapse as with oral prednisolone in management of acute asthmatic exacerbations management in patients discharged from the emergency department.

Keywords: Asthma, Dexamethasone, Prednisone, Relapse

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Introduction

Asthma is defined as reversible chronic inflammatory condition of lung airways resulting in airflow obstruction is known as Asthma. It is associated with hyper- responsiveness of airways and is the most prevalent chronic airway disease. Patients present most commonly with complaints of wheeze (expiratory) and intermittent dry cough most commonly. Older children report with shortness of breath (with inability to speak long sentences), chest pain and chest tightness. Asthma is one of the common reasons for emergency visits and hospitalization. The impact of asthma on quality of life of patients, as well as cost of management, is very high.[1,2] Therefore, early resolution of symptoms can have positive impact of quality of life and management cost.[3,4]

Systemic corticosteroids are important to reduce the severity of symptoms, duration of bronchodilator use and relapse rate.[3–5,5,6] There is always debate on short term use of systemic steroids especially prednisolone, it is widely used, is cost effective but it has issues of compliance and palatability. Whereas, shorter treatment duration of dexamethasone with longer half-life (72 hours), offers benefits of greater compliance over prednisolone.[7]

Studies report variable relapse rate of both dexamethasone and prednisolone. Objective of our study is to see if there is significant difference in relapse rate between dexamethasone and prednisolone after acute

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exacerbation of asthma in local settings.

Methods

This RCT was conducted in department of Pediatric Medicine from 15th April 2016 to 15th October 2016. Total 400 participants with acute exacerbation 2-12 years of age were included in current study. The population under study was randomly distributed in 2 groups. This distribution was made by random numbers table. Two hundred participants were included in oral dexamethasone group and 200 in oral prednisolone group. After standard treatment of acute exacerbation of asthma (nebulization with salbutamol) in emergency department group 1 was given 0.6mg/kg of tablet dexamethasone and for next 2 days and placebo agent for next 3 days, group II was given tablet prednisolone 2mg/kg in emergency and 1mg/kg/day for next 5 days. Severity of asthma was assessed by Pediatric Respiratory Assessment Measure (PRAM) score. After 2 weeks both groups were assessed in terms of relapse in asthma. Data was analyzed by SPSS-20. Follow up done in OPD or by phone.

Results

The mean age was 5.55±2.33 years in dexamethasone group while 7.57±2.37 years in prednisolone group. The mean duration of improvement of symptoms was 2.00±0.21 days in dexamethasone group and 2.00±0.48 days in prednisolone group (Table 1). Frequency and percentage of gender in both groups are shown in Table 2.

Table 1: *Mean±SD of patients according to Age and Duration of Improvement of Symptoms in Both Groups*

Variable	Dexamethasone group (n=200)	Prednisolone group (n=200)
Age (years)	5.55±2.33	7.57±2.37
Duration of improvement of symptoms (days)	2.00±0.21	2.00±0.48

Table 2: *Frequency and Percentage of Genders in Both*

Gender	Dexamethasone group (n=200)	Prednisolone group (n=200)
Male	103 (51.5%)	99 (49.5%)
Female	97 (48.5%)	101 (50.5%)

Table 3: *Comparison of Relapse in both Groups (n=400)*

Group	Relapse		P value
	Yes	No	
Dexamethasone	36 (18%)	164 (82%)	0.419
Prednisolone	30 (15%)	170 (85%)	
Total	66 (16.5%)	334 (83.5%)	

Relapse was seen in 18% cases in Dexamethasone Group as compare to 15% in Prednisolone Group (P=0.419) (Table 3).

Discussion

Asthma is one of the common reasons for emergency visits and hospitalization. Asthma has significant impact on quality of life in addition to posing an economic burden. Therefore, appropriate asthma management is warranted to minimize asthma related issues.[1,2,4,6]

Systemic corticosteroids (intramuscular/oral) help in reducing the severity of symptoms, duration of bronchodilator use, relapse rate and duration of hospital stay.[3–5,5,6,8] Some studies suggest shorter and lower dose of systemic steroids is less effective in managing exacerbation of asthma.[5]

There is always a debate on using short term systemic steroids especially prednisolone/prednisone vs dexamethasone. Prednisolone is widely used, is cost effective but associated with poor compliance and palatability. Dexamethasone has shorter treatment duration due to longer half-life (72 hours), and therefore better compliance and palatability.9 In this study, we compared relapse rate between prednisolone and dexamethasone.

Our results indicate that relapse rate was 18% in dexamethasone group as compare to 15% in prednisolone group (p=0.419). Dexamethasone exhibited 82% efficacy versus 85% with prednisolone in preventing relapses. This difference is statistically insignificant. In contrast to one retrospective study reported lower relapse rate with dexamethasone in comparison with prednisolone in asthma. In this study, there were 8769 patients, out of which 7130 received 5 days of prednisolone and 1639 received single dose dexamethasone. Disparity in sample size of both groups have impacted results.[10] Another study showed shorter length of hospital stay in patients receiving dexamethasone in comparison with prednisolone, which was not seen in our study.[11] Another study, used of single dose of dexamethasone vs 3 days of prednisolone in acute exacerbation of asthma in 226 patients. Day 4 PRAM score was same in both groups. Whereas, relapse rate in 2 weeks was higher in dexamethasone group 13.1% as compared to prednisolone group 4.2%.We failed to observe significant difference in relapse rate between

our groups.[12]

There are some studies showing comparable relapse rate in acute exacerbation of asthma, when single dose of dexamethasone is given as compared to 4 to 5 days prednisolone.[12,13] Likewise, there are many studies in which two doses of dexamethasone were compared with 5 to 7 days prednisolone with similar results, as were seen in our study.[4,6,7,14,15]

One RCT, compared 3 groups, 1st received treatment with single, low dose (0.3mg/kg) of dexamethasone, 2nd with two and higher doses (0.6mg/kg) of dexamethasone, 3rd received prednisolone 1.5mg/kg for 5 days. Relapse rate was found to be similar in all groups.[16] Likewise, a meta-analysis and systemic review showing comparable results in both groups as are seen in our study. But there is paucity of large clinical trials.[9] One study suggests dexamethasone has significant cost in comparison with prednisolone, while our study was not focusing cost of treatment.[17]

Limitations are single center study with small sample size. Further multicenter large clinical trails are required to suggest dose, duration of dexamethasone in comparison with prednisolone keeping in view compliance palatability and cost.

Dexamethasone has longer duration of action up to 72 hours, comparatively long half-life. It is palatable with less risk of nausea and vomiting as compared to prednisolone as shown by many studies.[3,7,9,15,18,19] This may offer an advantage in using it over prednisolone.

We found that prednisolone and dexamethasone both were effective without any significant difference in side effects. As a consequence, dexamethasone may be used as substitute to prednisolone because of shorter treatment regimens.

Conclusion

A 2-days course of oral dexamethasone has same frequency of relapse as 5-day oral prednisone in acute exacerbation of asthma.

Conflict of Interest: None

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Authors Contribution

Z F: Data CoIIection,

O A: Data Analysis

A I: Conception, Interpretation fo Data.

Esculapio - Journal of Services Institute of Medical Sciences

Original Article

Anti-Thyroid Peroxidase Antibodies in Euthyroid Pregnant Females to Detect Thyroid Autoimmunity

Ameelia Sadaqat,[1] Asim Mumtaz,[2] Nabeela Shami,[3] Usra Nazir[4]

Abstract

Objective: To show case the early appearance of anti-TPO antibodies, before the onset of thyroid hormone disruption.

Methods: It was a cross-sectional study in which 227 antenatal women who were euthyroid (normal free T4 and free T3 levels) were included and their Anti-TPO antibodies were analysed and recorded.

Results: The mean age of the pregnant females was 25.67 ± 4.531 years and the mean gestational age was 25.18 ± 9.214 weeks. Among 227 pregnant females, 97.8% had anti TPO antibodies levels in the 0-30IU/ml range while only 2.2% had >30IU/ml. The mean anti TPO level among pregnant females was 7.020 ± 4.004IU/ml. There was significant association ($p<0.05$) between trimesters and anti TPO Ab level while insignificant association ($p>0.05$) of anti TPO Ab with gravidity, parity and abortion.

Conclusion: Study concluded that adding anti-TPO antibodies together with markers of thyroid function such as TSH, FT4 and FT3 is not cost effective in identifying pregnant females who might develop thyroid dysfunction and associated pregnancy loss, preterm birth. The prevalence of Anti TPO Ab in euthyroid pregnant females in our study was only 2.2%.

Keywords: Anti thyroid peroxidase antibodies, thyroid-stimulating hormone, free thyroxin, euthyroidism, pregnancy

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Introduction

Thyroid hormones are of paramount significance when it comes to brain and somatic development among infants and of metabolic activity among adults. They have critical effect on the function of all organ systems.

The TAI (thyroid autoimmunity) seems to be an important determining factor in pregnancy loss. Several researchers have reported this relationship, not just among hypo or hyperthyroid females but also among euthyroid females.[1] There are three hypotheses that explain this relationship:

1. Thyroid antibodies can represent an indicator of a generalized autoimmune imbalance responsible for an enhanced frequency of miscarriage.
2. In spite of lab euthyroidism, females found to have thyroid antibodies positive prior to pregnancy can develop overt/subclinical hypothyroidism during the period of pregnancy. There is always a risk that a preexisting slight thyroid dysfunction can get worse during the period of pregnancy (particularly during 1st trimester). Thyroid antibodies effects among patients with thyroid disorders have been well recognized however their effect among euthyroid females is an arguable issue so far.
3. Because TAI shows a risk factor regarding infertility, females with antibodies are mostly older than those with no antibodies and that could explain

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the enhanced frequency of pregnancy loss.[2-4]

Euthyroidism is defined as normal thyroid function proven by normal serum levels of thyroid-stimulating hormone(TSH) and free thyroxin(FT4). Subclinical hypothyroidism is described biochemically as a normal serum free thyroxin (T4) concentration in the presence of a raised serum TSH concentration. There is a negative log-linear association between serum TSH and FT4 concentrations[1]. It means that very small alterations in the serum FT4 concentrations induce very large reciprocal alterations in the serum TSH concentrations. Consequently, thyroid function is best evaluated by measuring the serum TSH, assuming steady-state conditions.

In population-based researches, subclinical hypothyroidism prevalence ranges from 4-15%.[5,6] The incidence increases with increasing age and found elevated among women more than men as well as among whites more than blacks.[5-8] A study showed that frequency of the subclinical hypothyroidism was 4.2 percent in iodine-deficient region and 23.9 percent in a region with abundant iodine consumption, but high serum concentrations of anti-TPO antibodies.[9]

The Anti thyroid peroxidase antibody is the most prevalent anti-thyroid autoantibody, found in about 90 percent of Hashimoto's thyroiditis and 75 percent of the Graves' disease while 10-20 percent of the nodular goiter / thyroid cancer. Interestingly, 10-15 percent euthyroid persons can have elevated anti-TPO antibody titer levels.

Iodine is essential for normal thyroid function, and it can be acquired only by consumption of food that have it or to which iodine is added. During the period of pregnancy & lactation, iodine amount 250 mcg daily is recommended by WHO.

Thyroid hormone synthesis begins with iodine absorption. Nutritional iodine is absorbed as iodide and distributed quickly in extracellular fluid that also holds iodide discharged from thyroid gland and by the extra-thyroidal de-iodination of iodothyronines. The iodide leaves this pool via transport in thyroid and excretion in urine.[10]

Role of thyroid peroxidase(TPO) is very important. In thyroid follicular cells, iodide is transferred through pendrin to exocytotic vesicles combined with apical cell membrane.[1] The iodide in these vesicles is oxidized and organified to a few of the tyrosyl residues of thyroglobulin. This oxidation of iodide is catalyzed through TPO. Thyroxin(T4) is created by the coupling of 2 diiodotyrosine remains while T3 by the coupling of one diiodotyrosine and one monoiodotyrosine in a thyroglobulin molecule. These reactions are also catalyzed by TPO.

Approximately 75% of T4 is bound to TBG (thyroid binding globulin), 10% to TTR (transthyretin), 3% to lipoproteins and 12% to albumin. About 0.02% or 2ng/dL (25pmol/L), of T4 in serum is free.

For T3, about 80.0% is bound to the TBG and 15.0% to lipoproteins & albumin while 5.0% to TTR. Just about 0.5% or 0.4ng/dL (6pmol/L), of the T3 in serum is free. Production of TBG is increased 2-3 fold during pregnancy and T3 and T4 to about 30-100%[11] but free T4 and free T3 remain the same that is why it is essential to request free levels of T4 and T3 for accurate estimation of thyroid function[2-4]. The free hormone hypothesis states that the unbound or free hormone is the fraction that is available for uptake in the cells and for interaction with the nuclear receptors.

Approximately 1 in 10 pregnant women develop Thyroid autoimmunity in first trimester and roughly 16% develop subclinical hypothyroidism later in pregnancy.[12]

So, hypothyroidism may be predicted at the onset of pregnancy on the basis of TPOAb titers and TSH value, so that patients having TSH above 2.0 mIU/liter and/or high TPOAb (above 2000 kIU/liter) are more likely to develop overt thyroid dysfunction,[14] during pregnancy and more so during postpartum period, can be identified and put under vigilant surveillance.

The objective of the study was to evaluate the presence of anti-TPO antibodies in euthyroid pregnant females and predict onset of thyroid hormone disruption; hoping the addition of anti-TPO antibodies on top of traditional thyroid function markers TSH, FT4 and FT3 would aid to reduce untoward pregnancy outcomes and manage long-term morbidity.

Methods

It was a cross-sectional study conducted among antenatal women attending OPD of Ghurki Trust Teaching Hospital Lahore and Jinnah Hospital Lahore after approval of synopsis from the ethical review board of Lahore Medical & Dental College. The duration of study was 6 months. During study 450 pregnant women were selected with no history of known thyroid disease in self or in family. Five ml of blood sample was drawn, under aseptic conditions, from each subject for measurement of their serum free T3, free T4, TSH. The samples

were labeled and centrifuged within half hour. The serum of each patient was put into sterilized Eppendorf 5ml screw cap tubes. It was then transported to Chemical Pathology lab of Central Park Medical College Lahore in sample transport containers daily. The samples, which were not analyzed immediately were then stored at -20°C. Among these pregnant women, 227 were found to be euthyroid on the basis of operational definition and included in the study and their Anti-TPO antibodies were checked. Maglumi 800 chemiluminescence immunoassay (CLIA) system was used to measure serum FT3, FT4, TSH, Anti TPO antibodies in the collected samples. The tests were carried out in batches of 20 after collection. The normal range of Free T3(2-4.2pg/ml), Free T4(8.9-17.2pg/ml), TSH(0.3-4.5 uIU/ml) and Anti TPO Ab(0-30IU/ml) was considered according to the reagent used. Women taking drugs that could change thyroid levels, those with autoimmune disorders, chronic hypertension, diabetes mellitus, known thyroid disorder, with congenitally malformed fetus and not willing to take part in the study were excluded. A questionnaire was prepared containing age, trimester, obstetric history, TSH, FT3, FT4 and Anti TPO anti-bodies. The data was analyzed using SPSS version 24.0. Frequencies and percentages were calculated for qualitative data, while mean+SD was calculated for quantitative data. Chi-square test is not to determine the association. A P-value <0.05 was considered statistically significant. Confidentiality of the data was ensured and proper consent was obtained prior to data collection.

Results

Two hundred and twenty-seven women were euthyroid as their TSH was in range 0.3-4.5IU/ml and Free T4 was between 8.9-17.2pg/ml.

Among 227 pregnant females, 192 (84.6%) were 18-30 years old while only 35 (15.4%) were 26-45 years old. The mean age of the pregnant females was 25.67 $\pm$ 4.531 years.

Forty-one (18.1%) pregnant females were in their first trimester and 82 (36.1%) were in their second trimester while the majority 104 (45.8%) were in their third trimester. The mean gestational age was 25.18 $\pm$ 9.214 weeks as depicted by figure-1.

Out of 227 pregnant females, 87 (38.3%) were primigravidas and 140 (61.7%) were multigravidas. The mean gravidity was 2.20 $\pm$ 1.373.

Sixty-nine out of 227 pregnant females (30.4%), were primiparas and 59 (26.1%) were multiparas while only 3 (1.3%) were grand multiparas. The mean parity was 1.02 $\pm$ 1.165. Majority 189 (83.3%) had no abortion while 35 (15.4%) had 1-2 abortions and only 3 (1.3%) had >2 abortions. The mean abortion was 7.020 $\pm$ 4.004.

Among 227 pregnant females, 222 (97.8%) had anti TPO antibodies levels between 0-30IU/ml which is normal or negative, while only 5 (2.2%) had >30IU/ ml which makes them positive for TAI. This holds key significance in our study as shown in Figure-2. The mean anti TPO level among pregnant females was 7.020 $\pm$ 4.004. In the Anti TPO Ab positive group One (20%) was primigravida while four (80%) were multigravidas. There was no significant association between parity of females. Four females were Anti TPO Ab positive with no previous history of abortions. And one was positive with history of one abortion.

Figure-2 shows the association($p<0.05$) between trimesters and anti-thyroid peroxidase antibodies.

Table-1 demonstrates the association between thyroid function tests and different trimesters. Result shows that there was insignificant association ($p>0.05$) between thyroid function tests and different trimesters. But a significant association was found between Anti TPO Ab and different trimesters. Mean FT4 was 11.21$\pm$1.69 pg/ml, mean FT3 2.75$\pm$0.83pg/ml and mean TSH 1.53 $\pm$ 1.89uIU/ml.

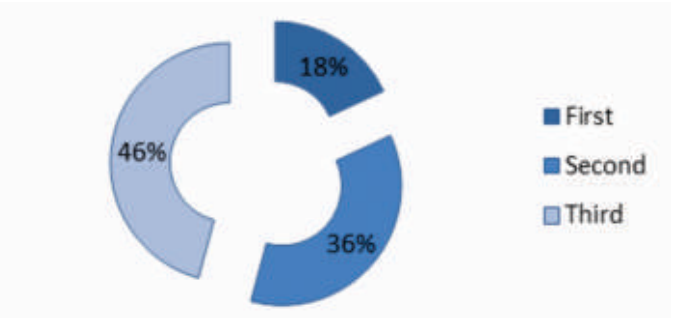

Figure-1: *Frequency Distribution of Pregnant Females According to Trimester*

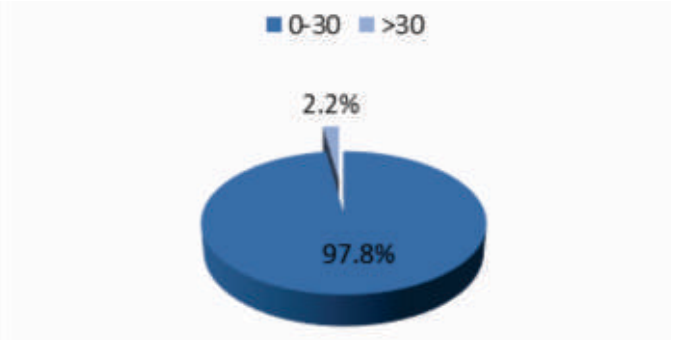

Figure-2: *Frequency Distribution of Euthyroid Pregnant Females According to Anti Thyroid Peroxidase Antibody(IU/ml)*

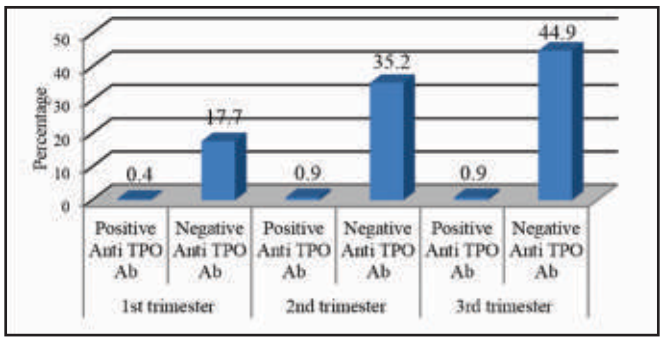

Figure-2: *Association between Trimesters and Anti-Thyroid Peroxidase Antibodies(IU/ml)*

Discussion

Anti-thyroid peroxidase antibodies are leading problem among pregnant females which increases the incidence of pregnancy loss, preterm birth. Present study "Anti Thyroid Peroxidase Antibodies in Euthyroid Pregnant Females" was carried out at Ghurki Trust Teaching Hospital Lahore and Jinnah Hospital Lahore. To acquire appropriate outcomes, 450 pregnant women were selected with no history of known thyroid disease in self or in family. TSH, Free T4 and Free T3 were performed. Among these pregnant women, 227 were found to be euthyroid on the basis of operational definition and included in the study. Anti-thyroid peroxidase antibodies were checked among these women.

Study revealed that 84.6% of the females were in 18-30 years age group while remaining 15.4% were in 26-45 years age group and mean age of the pregnant females was 25.67 ± 4.531 years. The findings of our study are almost comparable with a study undertaken by Elhaj and teammates (2016) who reported that mean age of the pregnant females was 27.0 ± 4.9 years.[13]

It was found during study that 45.8% of the pregnant females were in their third trimester, followed by second trimester (36.1%) and first trimester (18.13%). A study carried out in 2019 by Almomin and Mansour highlighted that most of the pregnant females (45.1%) were in their second trimester, followed by third trimester (30.3%) and first trimester (24.6%).[14]

Table 1: *Thyroid Function Tests and Antithyroid Peroxi-Dase Antibodies in different Trimesters, Mean and SD Ratio*

	Trimesters			Mean	P-value
	1st	2nd	3rd		
FT3 (pg/ml)	2.974± 0.975	2.912± 0.737	2.535± 0.930	2.751± 0.893	0.106
FT4 (pg/ml)	12.137 + 2.073	11.188+ 1.563	10.870+ 1.511	11.212± 1.699	0.177
TSH uIU/ml	0.928± 0.701	1.590± 1.248	1.723± 2.511	1.531± 1.898	0.090
Anti TPO Ab IU/ml	1.769± 9.297	3.979± 7.220	5.210± 8.004	7.020± 4.004	0.025

Thyroid disorders are common among pregnant females that increase the risk of abortion and other complications. Study disclosed that among pregnant females, mean gravidity was 2.20 ± 1.373 and mean parity was 1.02 ± 1.165 while mean abortion was 0.22 ± 0.558. The findings of a similar study conducted by Elhaj and teammates (2016) indicated that mean gravidity among pregnant females was 2.5 ± 4.0 while the mean parity was 0.8 ± 1.1.13

Study showed very encouraging results that among 227 pregnant females, major proportion (97.8%) had normal anti TPO Ab level (0-30IU/ml) and only 2.2% pregnant females were found positive for anti TPO antibodies(>30Iu/ml). The findings of our study are much better than a most recent study undertaken by Ning Yuan and Colleagues (2020) at Peking University International Hospital, who confirmed that 10.7% euthyroid pregnant females were found positive for anti TPO antibodies.[15] According to Almomin & Mansour (2019)[14]10.1% of their euthyroid pregnant females were Anti TPO Ab positive. Karuna et al (2017)[16] showed the study results in a different manor. Their Anti TPO positivity was 21.3% (49 0f 229) but out of these patients only 25 were euthyroid and 24 hypothyroid. So Anti TPO Ab positivity comes out to be 10.9%. Our Anti TPO Ab positivity rate in euthyroid pregnant females is far less than the above mentioned studies. On the other hand, a study conducted by Plowden et al shows a total positivity of 5.5% of Anti TPO Ab in their sample pregnant females.[17]

When the association between obstetric history and anti TPO antibody was assessed, no significant association (P>0.05) of anti TPO was found with gravida, parity and abortion. Kiran and fellows (2021)[18] also reported in their study that there was insignificant association (P>0.05) of anti TPO Ab with parity and abortion.[18] In another study, Karuna et al. (2017) found a two-fold rise in the pregnancy loss among TPO antibodies positive females when compared with TPO antibodies negative females. Though, the abortion rate in euthyroid females irrespective of thyroid peroxidase antibodies status was same (2.52% versus 3.06%).[16]

As far as association between trimesters and thyroid

function tests is concerned, study showed that there was insignificant association (P>0.05) between thyroid function tests and different trimesters. But a significant association was found between Anti TPO Ab and different trimesters. The increase in TSH mean levels was observed from first trimester to third trimesters while FT3 and FT4 mean levels were decreased from first trimester to third trimester. The mean levels of Anti TPO Ab were also increased from first trimester to third trimester. A similar study carried out by Elhaj and teammates (2016) showed an increasing trend from first trimester to third trimester for TSH but decreasing trend for FT3 and FT4 from first trimester to third trimester.[13] A study carried out by Elebrashy and cowor-kers (2019) indicated that Anti TPO Ab mean levels were decreased from first trimester to third trimester with significant results (P<0.001).[19]

Conclusion

Anti-thyroid peroxidase positivity is common problem among pregnant females. Study concluded that addition of anti-TPO antibodies together with traditional thyroid markers such as TSH, FT4 and FT3 is not cost effective in preventing pregnant females from thyroid dysfunction and associated pregnancy loss and preterm birth. American Thyroid Association Guidelines in pregnancy also indicate that there is insufficient data to recommend for or reject screening or treating all pregnant women for thyroid auto-antibodies

Conflict of Interest: None

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Authors Contribution

S A: Conceptualization of Project, Data Collection, Writing of Manuscript, Literature Search

M A: Data Collection, Statistical Analysis

S N: Drafting, Revision

N U: Literature Search

Esculapio - Journal of Services Institute of Medical Sciences

Original Article

Observation of Efficiencies of Different Off-loading Methods in Patients with Diabetes Mellitus and Forefoot Ulceration

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Abstract

Objective: Comparison between the groups of diabetic patients using total contact cast, accommodative dressing, a healing shoe, and a walking splint for healing of forefoot ulcers.

Methods: It is a Retrospective Study taking place in the Outdoor Department of General Surgery, Nishtar Hospital Multan, during 1st January 2020 to 15st April 2021.

A total of 164 patients were included in the study. Offloading was done in patients with the help of healing shoe, accommodative dressing which was fitted in a modified surgical shoe, a total contact cast (TCC), walking splint or combined methods that were termed as others. Different variables such as age, location of the ulcer, its depth, length, width and duration along with grading of diabetic foot (Grade I=superficial ulcer, Grade II=deep ulcer, Grade III=deep to the bone ulcer) [30] were used to adjust the overall healing time of the ulcer. Categorical variables were assessed by calculating their frequency and percentage while quantitative variables were assessed by calculating their mean and standard deviation. Chi square test was applied to assess the correlation among different variables. A P value of less than or equal to 0.05 was considered as statistically significant.

Results: Mean healing time was 33.84 ± 14.82 days in Total contact cast group; 26.89 ± 11.05 days in Accommodative dressing group; 32.17 ± 9.06 days in Healing shoes group; 39.96±13.06 days in Walking splint group and 41.54 ± 13.15 days in other treatment modalities group, and the difference was statistically significant ($p < 0.001$). Total 13 ulcers did not heal, one in Total contact cast group; 02 in Accommodative dressing group; 05 in Healing shoes group; 02 in Walking splint group and 03 in other treatment modalities group, and the difference was statistically insignificant ($p = 0.178$).

Conclusion: It can be concluded from the results of the study that use of customized dressings was significantly associated with decreased healing time in forefoot ulcers.

Keywords: Forefoot, Ulcer, Healing, Off-loading, Diabetic Foot, Total Contact Cast, Accommodative Dressings, Walking Splints.

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Introduction

More than 70% of diabetes-related lower-extremity amputations occur due to foot ulceration which is a serious complication.[1] Almost 15% of diabetic patients were reported to develop ulcerative foot once in the lifetime.[2] Causes of foot ulcer include loss of sensation and mechanical stress along with the walking stress which may enhance the incidence of injury.[3] Areas with highest pressure lead to plantar ulcerations which require removal of stress for healing the wounds.[3] There are number of suggested methods for removal of stress for healing foot ulcer.[4] The total contact cast has been reported to be effective method for reduction of the pressure in case of foot ulcer promoting wound healing.[5] It is considered as most effective method used for the wound healing and regarded as gold standard in the foot ulcer.[6] Due to special skills required for the fabrication and time taking method along with apparent risk for secondary injuries, the use of casts

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have not been common. Alternative to the casts which are made custom to fit the ulcerative foot includes healing footwear, foam dressings, walking splints, and accommodative dressings.[7] These devices are preferred because they offer local pressure over point of high pressure and reduce the pressure at lesion area as compared to prefabricated devices for ulcerations over the foot. Custom made devices include walking splints, custom-modified shoes, and wedged sole shoes proved to effective in the off-loading pressure and healing of wound at the site of ulcer over the foot.[8]

When compared to prefabricated shoes the custom-modified shoes proved to be more helpful in the reduction of pressure at the forefoot.[8] Studies are not present on the use of accommodative dressings for healing of wound but these are used for reduction of pressure on foot.[9] Current study revolves around the comparison between the group of diabetic patients using total contact cast and those using alternative custom made devices for pressure reduction such as accommodative dressing, a healing shoe, and a walking splint for healing of forefoot ulcers.

Methods

Diabetic patients presenting to the outdoor department of General Surgery, Nishtar Hospital Multan with primary complaint of neuropathic ulceration of the forefoot and treatment without surgery during 1st January 2020 to 31st May 2020 were included in the study. It is a retrospective study. Ethical approval for the study was obtained from the Ethical Board of Nishtar Hospital Multan. The sample size for this study was calculated using the reference study by Brike et al.[10] A non probability consecutive type of sampling technique was used. Patients with recurrent diabetic foot ulcer, postoperative lesion, osteomyelitis, ulceration on other parts of the foot (mid-foot, non-plantar, rearfoot), ulcers with abscess formation and ischemic wounds were excluded from the study. Patients were tested for neuropathy with 10g filament of nylon and had loss of sensation. A total of 164 patients were included in the study and their medical records were reviewed retrospectively. Offloading was done in patients with the help of healing shoe, accommodative dressing which was fitted in a modified surgical shoe, a total contact cast (TCC), walking splint or combined methods that was termed as others.

Use of walking splint and TCC was done according to the previously illustrated guidelines[11]. Healing shoe was a surgical shoe modified with non-polyethylene foam inlay while accommodative dressing was a six inches long adhesive felt which was quarter inch thick and it was attached over the fore-foot by making a cut-out on the ulcerated area. Furthermore accommodative dressing was modified by fitting it into the surgical shoe and with a wedged sole.

Other protocols such as antibiotics for cellulitis and use of moisture retaining dressings in all methods except TCC and accommodative dressings were followed as such. In TCC and accommodative dressings dry type of dressings was used. Changing of accommodative dressings was done weekly and TCC with 1 to 3 intervals while remaining patients were advised to change dressings daily. All patients were followed weekly for debridement of the wound and examination. Nineteen patients were applied with total cast, 39 with accommodative casts, 70 with healing shoes, 25 with walking splints and 11 with other off loading methods.

Ambulation of the patients was not controlled however patients were advised to use walkers etc for weight bearing ambulation. Data was collected by the researcher himself. Which patient will receive which method, was left to the discretion of the clinician. The largest ulcer on the forefoot was assessed for analysis of the outcomes. Different variables such as age, location of the ulcer, its depth, length, width and duration along with grading of diabetic foot (Texas University grading; Grade I=superficial ulcer, Grade II=deep ulcer, Grade III=deep to the bone ulcer)[30] were used to adjust the overall healing time of the ulcer.

All the data thus collected was subjected to statistical analysis using SPSS version 23. Categorical variables were assessed by calculating their frequency and percentage while quantitative variables were assessed by calculating their mean and standard deviation. Chi square test was applied to assess the correlation among different variables. A P value of less than or equal to 0.05 was considered as statistically significant.

Results

Patients were divided into five groups depending on their treatment modalities. There were no statistically significant differences in terms of mean age and gender distribution among the groups (p-value 0.072 and 0.088, respectively). Mean ulcer duration was 134.11±

50.07 days in Total contact cast group; 113.23 ± 41.91 days in Accommodative dressing group; 83.84 ± 33.74 days in Healing shoes group; 111.96 ± 47.93 days in Walking splint group and 101.55 ± 42.68 days in other treatment modalities group, and the difference was statistically significant (p <0.001). Table-I

There were no statistically significant differences

Table 1: *Group Characteristics*

Group	N	Age, years	Gender, M / F	Ulcer duration, days
Total contact cast	19	52.84±8.86	9 / 10	134.11±50.07
Accommodative dressing	39	58.05±6.65	21 / 18	113.23±41.91
Healing shoes	70	57.71±6.68	26 / 44	83.84 ± 33.74
Walking splint	25	57.24±6.56	8 / 17	111.96 ± 47.93
Others	11	58.54±7..27	8 / 3	101.55 ± 42.68
p-value	-	0.072	0.088	<0.001

observed among the groups in terms of Wagner grade, length of ulcer, width of ulcer and depth of ulcer (p-value 0.464, 0.305, 0.935 and 0.850, respectively). Table-II

Table 2: *Ulcer Characteristics*

Group	Wagner grade	Length, cm	Width, cm	Depth, cm
Total contact cast	1.95 ± 0.78	2.95 ± 1.26	1.89 ± 0.73	0.82 ± 0.36
Accommodative dressing	1.87 ± 0.80	3.02 ± 1.20	1.95 ± 0.72	0.79 ± 0.37
Healing shoes	1.91 ± 0.77	2.96 ± 1.16	1.98 ± 0.73	0.85 ± 0.38
Walking splint	1.96 ± 0.79	3.01 ± 1.15	1.88 ± 0.72	0.79 ± 0.35
Others	1.91 ± 0.83	2.18 ± 0.98	1.82 ± 0.75	0.91 ± 0.38
p-value	0.464	0.305	0.935	0.850

Mean healing time was 33.84 ± 14.82 days in Total contact cast group; 26.89 ± 11.05 days in Accommodative dressing group; 32.17 ± 9.06 days in Healing shoes group; 39.96±13.06 days in Walking splint group and 41.54 ± 13.15 days in other treatment modalities group, and the difference was statistically significant (p <0.001). Total 13 ulcers did not heal, one in Total contact cast group; 02 in Accommodative dressing group; 05 in Healing shoes group; 02 in Walking splint group and 03 in other treatment modalities group, and the difference was statistically insignificant (p =0.178).

Wound closure at 12 weeks was observed in 95% of Total contact cast group; 95% of Accommodative dressing group; 77% of Healing shoes group; 76% of Walking splint group and 64% of other treatment modalities group, and the difference was statistically significant (p =0.028). Table-III

Table 3: *Comparison of Healing Time*

Group	Healing time, days	Not healed, N	Closed at 12 weeks, %
Total contact cast	33.84 ± 14.82	1	95%
Accommodative dressing	26.89 ± 11.05	2	95%
Healing shoes	32.17 ±9.06	5	77%
Walking splint	39.96 ± 13.06	2	76%
Others	41.54 ± 13.15	3	64%
p-value	<0.001	0.178	0.028

Discussion

This study was conducted for determination of effectiveness of alternative methods of off-loading the pressure from the different grades of ulcerative foot[30]. when compared these devices to the total contact casts for the purpose of healing of wound. Findings of the studies suggested that the diabetic patients with forefoot ulcer in which custom made devices (an accommodative dressing, fit in a modified surgical shoe, healing shoe, or walking splint) were used had better rates of wound healing by off-loading pressure than those in which total contact cast was used. Clinicians selected of the method of off-loading, which required different factors to be considered such as preference of patient, severity of symptoms, patient's mobility, compliance of patient to the method, and time required for fabrication. Time required for healing may also be affected by these factors and use of different types of topical dressings for different methods of off-loading may also effect the healing. These uncontrolled factors were the major limitations in this study while identifying the most effective off-loading method.

Different aspects such as area of ulcer, age of patient, and duration of ulcer were taken under account before selection of the methods of off-loading. However for off-loading of plantar ulcers total contact cast was regarded as gold standard method by the authors. As our study included the diabetic patients of young age and total contact cast was used for ulcer located at metatarsal area only. For toe ulcer the healing shoe was a preferred method of offloading. In this study combination of accommodative dressing and modified surgical shoe were used but studies must determine

the effect of each method separately in ulcer healing.

Our study revealed that the healing progress was 24% in 12 weeks which is much higher than the studies in which no customized method was used with standard wound care for off-loading.[12] Implementation gap between off-loading techniques used in both studies, or poor professional training for use these techniques lead to this difference in the outcomes. These findings highlight the requirement of effective off-loading methods that can be used by the medical related personals managing foot ulcer including nurses, podiatrists and physical therapists.

In a study done by David et al.,[13] findings suggested that total contact cast was more effective in wound healing and require less time for healing as compared to the other off-loading methods including removable cast walker and half shoe. In other studies it was reported that by the use of total contact casts time required for healing of ulcer was only 6-8 weeks.[14] High percentage of wound healing was reported in descriptive and randomized clinical trials by the use of total contact cast than that of topical growth factors, bioengineered tissue, or special dressings.[15,16,&18]

Current study involved the analysis of different off-loading methods used for ulcer healing in diabetic patients in order to determine the most effective method for meeting the requirements at different levels of population and clinical disciplines and settings. Accommodative dressing and the healing shoe were two off-loading methods used in this study providing custom relief to the ulcer area, needed simple fabrication thus require less training and less time to apply it over the ulcerative foot as compared to total contact cast. For prevention from further injury and effective off-loading care must be taken while applying any technique. Less difference of the healing time by the use of different techniques used by two different clinicians in this study supported the general effectiveness of these methods.

Conclusion

It can be observed from the results of the study that use of accommodative dressings like customized dressings was significantly associated with decreased healing time in forefoot ulcers.

Conflict of Interest: *None*

Funding Source: *None*

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Authors Contribution

M A: Conceptualization of Project
M I: Data Collection
J U R: Literature Search
Z I M: Statistical Analysis
M K J: Drafting, Revision
K H Q: Writing of Manuscript

Esculapio - Journal of Services Institute of Medical Sciences

Original Article

Fetal Outcome In Pregnant Females Presenting In Preterm Labour With Mitral Stenosis

Hira Naeem,[1] Madeeha Rashid,[2] Muhammad Usman,[3] Maria Khalid,[4] Salma Khalid,[5] Rubina Sohail[6]

Abstract

Objective: To determine the fetal outcome after delivery in pregnant females presenting in preterm labour with mitral stenosis during pregnancy.

Methods: We conducted descriptive study in Unit II, Department of Obstetrics & Gynecology, Services Hospital, Lahore from 23-12-2017-to-22-12-2018. Total 136 females who fulfilled the inclusion criteria were enrolled in the study. After detailed information and consent, demographic profile and gestational age were noted then preterm birth (<37weeks) was labeled. After delivery, fetal outcome was scrutinized by weight (<2.5 kg) at the time of birth and APGAR score (<7).

Results: Mean age of women in this study was 28.64±6.32years. Mean gestational age was 35.26±2.37weeks. Among women 48(35.3%) were primigravida, 58 (42.6%) women were para 1 and 30 (22.1%) women were para 2 or above. Preterm delivery was seen in 47(34.6%) women. Poor Apgar score was seen in 41(30.1%) cases and 51(37.5%) mothers had Low birth weight neonates.

Conclusion: Low birth weight was the most frequently observed outcome in women who presented with Mitral stenosis followed by preterm delivery and Poor APGAR score.

Key Words: Pregnancy, Mitral stenosis, Valvular heart disease, Low birth weight, APGAR score, Preterm delivery.

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Introduction

Pregnancy complicated with cardiac disease is classified as High Risk Pregnancy. Increased cardiac demand is a physiological change in pregnancy which is considered to increase the morbidity and mortality in females who are already having a cardiac disease.[1]

Cardiac diseases complicate from 0.1% - 4% of pregnancies. In Low and middle income like Pakistan, rheumatic heart disease is most common cardiac ailment with mitral stenosis being most common Valvular lesion.[2] Physiological changes of pregnancy mimic the symptoms of complications of cardiac disease and so pose a diagnostic difficulty to obstetricians.[3,4] The physiological changes in cardiovascular system in pregnancy continue to happen throughout pregnancy but these are more in first trimester. Symptoms of mitral valve disease manifest usually when mitral valve area is decreased to 2cm^2, which is normally about 4-6cm^2. Echocardiography is the key investigation in diagnosing the condition.[5] Cardiac disease in the pregnant female can pose cha-llenges in cardiovascular and fetomaternal management. It is important to know that even in normal females, pregnancy imposes some aggressive physiologic chan-ges upon the cardiovascular system.[6] Less insight into pathophysiology and simultaneous pregnancy complications make the outcome of pregnancy even poor. Incidence of fetomaternal morbidity and mortality can be downed with proper antenatal, intrapartum and postnatal care in association with cardiologist and pediatrician.[7]

Preconception counseling, risk assessment and optimi-

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zation of cardiac disease before pregnancy are the key factor in reducing the incidence of fetomaternal complications in females suffering from valvular heart lesions.[2,8] According to some literature, patients whose valvular lesion is uncorrected or severe (NYHA III and IV) before pregnancy, and patients who are on anticoagulant therapy must not get pregnant. Recognition of adverse complications of pregnancy, in terms of heart disease and neonate, are of vital importance. It is also stressed to identify antecedent risk factors having the potential of prognosticating the probability of poor perinatal outcome.[9] By doing this research we will address fetal outcome in women whose pregnancy is complicated with mitral stenosis (NYHA I, II and III) and strategize the best management for these patients.

Methods

The study was run in Unit II, Gynaecology & Obstetrics Department, Services Hospital of Lahore. This was a descriptive case series for one-year duration from 23-12-2017 to 22-12-2018. Ethical approval was taken from IRB of hospital. After informed consent total 136 females accomplishing the inclusion criteria were included in the study. Non probability, consecutive sampling technique was used. Sample size of 136 cases is calculated with confidence level of 95%, margin of error of 5% and expected percentage of low APGAR score taking as 14.9% in pregnant females presenting with mitral stenosis. Patients of age 18-40 years, having singleton pregnancy (on USG) after 32 weeks of gestation calculated from last menstrual periods who presented in active labour (>3contractions in 10 minutes, >4cm cervical dilatation) with diagnosis of mitral valve Stenosis were enrolled in study. Un-booked females having pregnancy with medical disorders, mitral stenosis comorbid with other cardiovascular or Valvular disease, cardiomyopathy and fetus with congenital anomalies were excluded from study. Demographic profile like age, gestational age and parity were noted. The gestational age was determined and preterm birth (<37weeks) was labeled. After delivery, APGAR score was noted and birth weight of neonate was obtained. Assessment of fetal outcome was done in terms of poor APGAR score and low birth weight. Data was recorded using pre designed Performa. SPSS version 20 was used to analyze all the data. Mean and standard deviation was calculated for the quantitative variables like age, BMI and gestational age. Frequency and percentage was calculated for the qualitative variables like outcome i.e. preterm birth, LBW, and poor APGAR score. Parity was also presented as frequency. Data was stratified for age, parity and gestational age. Chi-square test was used to compare outcome in stratified groups. P-value<0.05 was considered as significant.

Result

In study mean age of woman was 28.64±6.32years. Mean gestational age of women was 37.86±2.37 weeks. Among women 48(35.3%) were primigravida, 58 (42.6%) women's parity was 1 and 30(22.1%) women's parity was >2. Preterm delivery was seen in 47(34.6%) women. Poor Apgar score was seen in 41(30.1%) cases. LBW of neonates was observed in 51(37.5%) cases. Age & parity of patients had no significant effect on preterm delivery (p>0.05, except Gestational age (p< 0.05). Age & parity of patients had no significant effect on Poor APGAR score (p>0.05, except Gestational age (p<0.05). Age & parity of patients had not significant effect on LBW (p>0.05, except Gestational age (p<0.05).

Demographics

Table 1: *Frequency of Preterm Delivery, Poor Apgar Score& Low Birth Weight*

Indicators	N=136 Frequency	Percentage (100%)
Preterm delivery		
Yes	47	34.6%
No	89	65.4%
Poor Apgar score		
Yes	41	30.1%
No	95	69.9%
Low birth weight		
Yes	51	37.5%
No	85	62.5%

Table 2: *LBW Stratified for Effect Modifiers*

		LBW		p-value
		Yes	*No*	
Age	18-25	20(41.7%)	28(58.3%)	0.669
	26-32	14(32.6%)	29(67.4%)	
	>32	17(37.8%)	28(62.2%)	
Parity	Primigravida	17(35.4%)	31(64.6%)	0.711
	Parity 1-2	24(41.4%)	34(58.6%)	
	Parity >2	10(33.3%)	20(66.7%)	
Gestational Age	≤37	25(53.2%)	22(46.8%)	0.006
	38-41	26(29.2%)	63(70.8%)	

Discussion

Women in reproductive age with heart disease pose a serious challenge to the medical professional. The

Table 3: *Preterm Delivery and Poor APGAR score Stratified for Effect Modifiers*

		Preterm delivery		p-value	Poor APGAR score		p-value
		Yes	*No*		*Yes*	*No*	
Age	18-25	13(27.1%)	35(72.9%)	0.201	15(31.3%)	33(68.8%)	0.554
	26-32	14(32.6%)	29(67.4%)		15(34.9%)	28(65.1%)	
	>32	20(44.4%)	25(55.6%)		11(24.4%)	34(75.6%)	
Parity	Primigravida	15(31.3%)	33(68.8%)	0.762	15(31.3%)	33(68.8%)	0.366
	Parity 1-2	22(37.9%)	36(62.1%)		20(34.5%)	38(65.5%)	
	Parity >2	10(33.3%)	20(66.7%)		6(20.0%)	24(80.0%)	
Gesta-tional Age	≤37	47(100%)	0(0.0%)	0.000	26(55.3%)	21(44.7%)	0.000
	38-41	0(0.0%)	89(100%)		15(16.9%)	74(83.1%)	

pregnancy or physiological variations predisposes cardiac patient to deteriorate. Treating pregnant females with valvular lesion of heart is a hard work for obstetricians. Although the risk factors in patients with cardiac disease have been recognized, but there is no good evidence as large scale studies, specially randomized controlled trials are lacking.[10]

During pregnancy, the cardiovascular system undergoes exuberant changes in terms of hemodynamics. Healthy females tolerate these cardiovascular changes very well, but significant morbidity and mortality is reported in pregnant females who have cardiac disease.[11] Pre-eclampsia, anemia, pre-term labour, and intra uterine growth retardation are frequently reported in pregnant females with cardiac disease, that even worsen the outcome and complicate the management. In order to improve the fetomaternal outcome in pregnancy by providing up to the mark antenatal care, an extensive assessment of pregnant females should be done for some veiled cardiovascular disease.[7]

In this study 34.6% mothers had preterm delivery. Studies from India have reported preterm delivery among women with cardiac disease as 10-27.7%.[7,8] However local studies form Pakistan reported preterm delivery among women with cardiac disease as 14-21.8% respectively.[2,12] Results of this study regarding preterm delivery is comparable with the studies from India and Pakistan.

Poor APGAR score was seen in 41(30.1%) neonates in our study. A local study reported frequency of poor APGAR score as 14.9% and an Indian study reported the Poor APGAR score as 10% in women who presented with cardiac disease.[2,7] In study conducted by Salam S reported Poor APGAR score in 75% of women with heart disease. [13]

Reasons of high frequency of Poor APGAR score was due to lack of proper preconception care with poor follow up with cardiologist and starting pregnancy with already decompensated status, predisposes our patient towards adverse fetal outcome. In order to improve fetal outcome in cardiac patients, they must be treated with a multidisciplinary approach. Pre conception risk assessment, optimization of the disease for pregnancy and counseling of couple regarding anticipated risks should be done in order to improve fetomaternal outcomes.

In this study 51(37.5%) mothers had LBW neonates. In study conducted by Nazia incidence of low birth weight neonates was 27.7% who were born to mothers with mitral stenosis.[2] Naila Yasmeen in her study reported frequency of LBW as 40% which is a bit higher as that of this study.[10]

Extent of maternal wellbeing and duration of pregnancy are main predictor of fetal outcome. In pregnant females with NYHA grade I &II disease, perinatal outcome was good, while in females with NYHA grade III & IV disease, poor perinatal outcome was reported with death rate of 12% - 31%.[14]

In pregnant females with cardiac disease, increase incidence of preterm deliveries, low birth weight and poor APGAR score was found specially in females who had moderate and severe Mitral valve stenosis. Valvular stenosis leading to hemodynamic compromise which decreases utero-placental circulation and is a logical explanation of poor fetal outcome. The incidence of preterm delivery, low birth weight and intrauterine growth retardation was less in females with valvular cardiac disease but were maintaining good cardiovascular parameters. Maternal morbidity and mortality were also reduced.[15]

Conclusion

This study concluded that among pregnant females with mitral stenosis, the most common outcome was low birth weight, followed by preterm delivery and poor Apgar score. Proper pre-conception assessment of woman regarding cardiac disease and proper antenatal care are key measures to achieve desired pregnancy outcome in these pregnant females. From this study we reached a conclusion that pre-conception diagnosis and optimization, counseling, referral to specialized centre, tailored antenatal care and intrapartum care at multidisciplinary center can improve the fetomaternal outcome in pregnancy complicated with heart disease.

Conflict of Interest: *None*

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H N, R S: Conceptualization of Project
H N, M K, S K: Data Collection
H N, M R: Literature Search
H N, M R, M U: Statistical Analysis
H.N, M.R: Drafting, Revision, Writing of Manuscript

Esculapio - Journal of Services Institute of Medical Sciences

Original Article

Changing Trend in Clinical Spectrum of Salmonella Typhi in Children

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Abstract

Objective: To determine the clinical spectrum and outcome of enteric fever in children.

Methods: It was a descriptive cross-sectional study conducted in Services Hospital, Lahore from 1 January 2021 till 31st July 2021. It included all patients in the age group of 1-18 years who were clinically suspected to have enteric fever. Non-probability consecutive sampling was used. Clinical features and their outcome were recorded on a predesigned proforma. Blood cultures were obtained from all patients and tested microbiologically by standard procedure.

Results: This study included 355 patients. 200 were male and 155 were females. 45 patients were from 1-2 years, 2-5 yrs (83), 6-10 yrs (95) and 11-18 yrs (132). Fever (100%) was seen in all patients followed by anorexia (91%), abdominal pain (85%), vomiting (63%), diarrhea (56%), constipation (28%) and cough (30%). 25% cases presented with high fever on first day of illness. Common physical findings were coated tongue (77%), splenomegaly (49%) and bradycardia (42%). Complications were present in 5% of cases. Blood culture was positive in 36 (10%) patients. Among them 25 patients showed extensive drug resistance.

Conclusion: A change in clinical spectrum of salmonella typhi is manifesting over last few years. It has now been seen in infants and classical step ladder pattern of typhoid fever is rarely seen. Cough along fever is notably present in enteric fever. Drug resistance is a major threat and introduction of TCV vaccine in our EPI schedule for infants and children can reduce the disease burden.

Key words: Clinical spectrum, Outcome, Enteric fever

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Introduction

Enteric fever is a common public health problem in developing countries.[1] The main causative organism is S. Typhi, which is a gram-negative rod. However, Salmonella Paratyphi A and rarely S. Paratyphi B and Paratyphi C have also been seen as the cause of this illness. In 2017, statistics collected from all over the world showed that 14.3 million people were sufferers of typhoid fever during that year[2] that caused 135.9 thousand deaths with main bulk (69.6%) from South Asia.[2] Enteric fever is widespread in poor income regions in South Asia, including Pakistan, because of lack of clean drinking water and dirty hygienic and sanitation services.[3,4] During a recent study in Karachi, a high incidence of enteric fever has been reported in children in Pakistan, with rates as high as 1000 cases per 100000 child per year.[5]

The transmission of this illness is through orofecal route and its incubation period varies from 7-14 days and can be as short as 3 days and can extend up till 30 days depending upon the infecting dose. The organism after reaching the lymphoid tissue of the small bowel, involves the Payer's patches which get swollen, and then ulcerate and finally gets healed. Approximately 5% of the patients become chronic carriers especially when gall bladder is involved and release bacteria in feces commonly and rarely in urine after clinical resolution.[6]

Enteric fever involves a varied clinical presentation

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ranging from low-grade fever, malaise, to a more severe disease involving pain in abdomen, high grade fever, decrease oral intake, jaundice, coated tongue, body aches, hepatosplenomegaly. In children, constipation may occur after diarrhea. The clinical picture is more diverse in children under five years of age. If no complications occur, the symptoms and physical findings gradually resolve within 2-4 weeks.

Earlier on typhoid fever was used to be treated by ampicillin, chloramphenicol and co-trimoxazole (first line drugs). Over last two decades S. typhi Genotype Hn58 has evolved in various parts of the world which is resistant to first line drugs; multi drug resistant (MDR) typhoid fever.[7] In 2016, a new strain of salmonella typhi HN58 which is resistant to all five drugs, ampicillin, chloramphenicol, co-trimoxazole, ceftriaxone and quinolones was found in Pakistan. This resistant strain has been labeled as extended drug resistant strain (XDR Typhoid fever).[8] Its first epidemic was reported in November 2016 in Hyderabad which next year got evolved to Karachi. More than 10,000 cases were reported in July 2019 in Hyderabad and Karachi. This resistant strain (XDR salmonella) is gradually spreading to other cities and it has also been isolated in Pakistani travelers to other countries as well.[9]

Few studies have been conducted regarding clinical spectrum of typhoid fever with XDR salmonella strain in Lahore.[10] Local literature is also scarce on out come and clinical response following antimicrobial use in this group of resistant typhoid fever. This study will help to understand clinical behavior and response to therapy of XDR S. typhi Hn58.

Methods

It was a descriptive cross-sectional study conducted in Pediatric Department and Pathology Department of Services Hospital, Lahore from 1st January 2021 till 31st July 2021. After ethical approval from hospital authority, all the patients in the age group of 1 to 18 years with clinically suspected enteric fever were included in this study. Non- probability consecutive sampling was used. Case definition of suspected typhoid fever is a patient with documented fever (38°C and above) for at least 5 days prior to presentation, with rising trend in clinic and having no other focus to explain the cause of the fever (e.g. UTI, pneumonia, abscess etc.) OR a clinically compatible case that is epidemiologically linked to a confirmed case of typhoid fever.[11] A detailed account of clinical features were recorded on a Proforma, especially designed for this purpose. All patients were subjected to detailed history and examination. Blood cultures were done in all patients after taking proper aseptic measures. Salmonella strains were tested for their sensitivity to eight antimicrobial agents by disc diffusion method and were incubated at 37°C for at least 7 days.

All patients were given treatment in the form of IV fluids, anti-pyeritics, anti- emetics as and when needed. Empirical treatment started with cephalosporins (Oral Cefixime or IV Ceftriaxone) until blood culture results were available. Patients were switched to IV cephalosporins or fluoroquinolones, if there were no clinical signs of improvement after 5 days of treatment or any signs of complications appear. Final antibiotic regime depends on the culture and sensitivity report. Outcome was determined in the form of completely cured, referred and expired. The data was recorded in SPSS version 20 and Data has been summarized using percentages and frequencies.

Results

This study included 355 patients. Out of these 200 were male and 155 were females shown in table 1. Among them 45 were from 1- 2 years of age, 83 were from 3-5 years of age, 95 were from 6 to 10 years of age and 132 were from 11-18years of age. The age distribution is shown in figure 1 below.

Table 1: *Gender Distribution*

Gender	No. of patients	Percentage
Male	200	56%
Females	155	44%

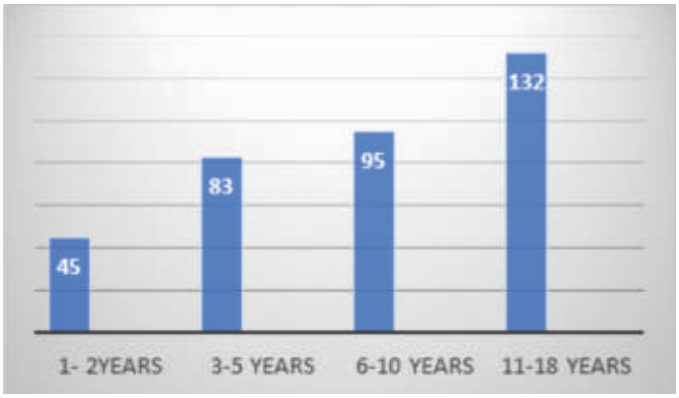

Figure 1: *Age Distribution*

The most common presenting symptom in our study was fever (100%). High fever >101°F on first day of illness was seen in 25 % case (107/355case). Second common feature was anorexia which was seen in (91%) followed by abdominal pain (85%), vomiting (63%),

diarrhea (56%) and constipation (28%). Cough was a prominent feature in (30%). Least common presenting symptoms were headache (14%) and rash (2.8%) The most common physical finding was coated tongue (77%) followed by splenomegaly (49%) and bradycardia (42%). Least common findings were rose spots (4%) and acute abdominal pain (14%). Complications at the time of admission or during treatment in hospital, were seen in eighteen patients (5%). Adynamic ileus was present in fifteen patients (4%), shock at the time of presentation was present in two patients (0.5%) and intestinal perforation in one patient (0.2%).

Positive blood cultures were seen in 10% of cases and all isolates showed salmonella typhi. All culture positive cases were resistant to ampicillin and chloramphenicol while sensitivity to ceftriaxone was 22% and to ciprofloxacin was 8% (MDR). However, sensitivity to azithromycin, meronem and imipenem was 100%.

Antibiotic sensitivity pattern of culture positive cases has been shown in table 2.

All patients enrolled in the study completed their course of illness successfully. They were being monitored for their signs and symptoms and were given treatment accordingly. All patients were cured, including those who developed complications and were discharged back home with no mortality.

Table 2: *Antibiotic Sensitivity Pattern of Culture Positive Cases*

Antibiotic	Sensitive no. of patients	Percentage
Meronem	36	100%
Imipenem	36	100%
Azithromycin	36	100%
Ceftriaxone	8	22%
Ciprofloxacin	3	8%
Chloramphenicol	0	0%
Ampicillin	0	0%

Discussion

In under developed countries, enteric fever has become a big challenge. In recent past, its clinical behavior is changing which has made its clinical diagnosis difficult. In our study at Pediatric Department SIMS Lahore, we have also found a change in its clinical spectrum. Due to its varied clinical manifestations, it is often found to be confused with other infections. Previously typhoid fever used to be considered a disease of toddlers and older children as payers' patches were not well developed in infants thus infants were taken as not a victim of salmonella infection. In our study 45 cases were 1-2 years old. Decreasing trend of breast feeding and injudicious use of weaning foods may be the reason. Our study showed increased incidence of infection in boys. Same results were obtained from other disease prevalent areas.[12-13] Although there is no scientific reason for this, however most relevant explanation could be relatively more outdoor contact, consuming eatables from out, and activities, and attitudes of boys resulting in increased risk for S. Typhi infections in low-income countries.[13] Another reason could be more healthcare seeking for boys by parents.

In our study we found that increase number of cases were reported during the months of April till September with highest number of cases with rainfall as compared to winter season. It has been seen that wet weather conditions and rainfall has major impact on the occurrence of typhoid.[14] Sanitary and drainage system of slums is at worst situation in rainy season.

In our current study, Fever was seen in all (100%) patients. 25% cases (107/355) presented with high fever >101 F on first day of illness. Typical step ladder pattern was not described by most of the patient. Similar results were seen in studies conducted in Karachi and India.[15,16] Other clinical features that are commonly found in enteric fever are anorexia, vomiting, diarrhea, constipation, headache and abdominal pain. We noted anorexia in 325 (91%) patients and headache in 13% cases that was consistent with results of study done in Srinagar.[17] Diarrhea was seen in 100(28%) patients which is consistent with the results obtained from another study conducted in India,[16] however abdominal pain was found in 14 cases (18.4%) and Vomiting was seen in 225 (63%) patients that was in contradiction to the similar study conducted in India.[16] Constipation was seen in 28% cases in our current study that was in contradiction to study conducted in Canada.[18] This can be due to undue restrictions imposed by general practitioners and family taboos in our country. Similarly, coated tongue was found in 77% of cases that is a higher percentage as compared to a study done in Gujrat in India.[19] In the same way splenomegaly was found in 49% of cases that is again a higher percentage as compared to another study conducted in India.[20] This depicts higher degree of bacteremia and septicemia in our study cases. These results showed that enteric strain is evolving and changing its spectrum over time.

Clinical outcome was measured as defervacence (decline of fever), improvement in oral feeding, and deve-

lopment of any complication, mortality or discharge time from hospital. Complications were seen in only 5% of patients and was seen in those with XDR and those who belong to under 10 years age group. All patients were given treatment initially with cephalosporins, however those who did not responded over 5 days or developed complications or culture and sensitivity showed resistance to cephalosporins were shifted to second or third line antibiotic depending on the culture and sensitivity report. All patients in this study were recovered and discharged. Similar results were obtained from a previous study conducted in Pakistan regarding mortality due to typhoid.[21] However, a study conducted in Vietnam reported 2% mortality secondary to S. Typhi among hospitalized patients.[22]

Blood culture was positive in only 10% of patients (35 cases). This relatively lower percentage of culture positivity could be due to the prior use of antibiotics before sending the blood cultures. All culture positive cases were resistant to first line treatment of enteric fever. This is in contradiction to previous studies where sensitivity to ceftriaxone and quinolones was high[23]. However, sensitivity to ceftriaxone was only 22% and to ciprofloxacin was 8% (11 cases MDR typhoid fever) and azithromycin, meronem and imipenem were 100% sensitive (24/35 cases XDR Typhoid fever). A study conducted in Bangladesh showed 100% sensitivity to azithromycin.[24] This alarming and new trend in antimicrobial resistance in S. Typhi demands a rapid action at the international level. If no action will be taken we will be left with only few antibiotic choices for the effective treatment of enteric fever, which will not only raise the cost of treatment but will also, increase the mortality and complications of the disease.

This study puts emphasis on the use of vaccination and other protective measures in our country. In 2019, a mass TCV immunization campaign was conducted for children aged 9 months to 15 years of age in Sindh province and in 2020 in Punjab as well. It is a high time to introduce this vaccine in our vaccination program for all children at 9 months of age in other parts of the country. It will be effective in decreasing the disease burden.

Conclusion

Enteric fever is a very common infection in Pakistan. With the rise of XDR cases, it is time to take urgent measures at national level such as clean drinking water, environmental hygiene, and sanitation to deal with this public health problem. Vaccination of children against typhoid fever is another short term solution. Blood culture yield can be increased by drawing sample prior to administration of antibiotics. Significant emphasis should be put on the introduction of TCV vaccine in our EPI schedule for infants and children to reduce the disease load.

Conflict of Interest: *None*

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Authors Contribution

FT: Conceptualization of Project,Data CoIIection, Literature Search, Writing of Manuscript, Drafting, Revision

F T, R S, T R: Data Co11ection,

F T, T R, S L: Literature Search

F T, A Z, S A B: Drafting, Revision

F T, R S U: Writing of Manuscript

Esculapio - Journal of Services Institute of Medical Sciences

Original Article

Role of Antiplatelet Therapy For Prevention of Preeclampsia in High Risk Patients

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Abstract

Objective: To assess the efficacy of antiplatelet therapy to prevent pre eclampsia in high risk patients.

Methods: This descriptive case series study was carried out at Sir Ganga Ram Hospital, Lahore for duration of 6 months (from 28-11-2018 to 28-05-2019). Total 200 women were enrolled in the study fulfilling the inclusion criteria.Their demographic details were obtained after informed consent.All participants were given 120 mg/day of antiplatelet (Asprin), (NICE Guideline 107).They were followed-up in OPD till 36th week of gestation. If female developed BP≥140/90mmHg and proteinuria> 300mg on urine dipstick method, then preeclampsia was labeled. All this information was recorded on predesigned Performa. Complications of antiplatelet therapy like antepartum hemorrhage, acid peptic disease and low platelets were also recorded.

Results: The mean age of all females was 29.87 ± 5.82 years. There were 12(6%) females who had preeclampsia in previous pregnancy, 45(22.5%) were obese cases,16(8%) females had chronic hypertension, 138(69%) females had gestational hypertension and 37(18.5%) cases had gestational diabetes. The complications observed were preeclampsia in 25 (12.5%) cases, hemorrhage in 94(47%), acid peptic disease in 64(32%) and low platelet in 17(8.5%) cases.

Conclusion: It is concluded that the frequency of preeclampsia was very low among high risk females after having 120mg of Aspirin (antiplatelet therapy) in first trimester but the side effects of antiplatelet therapy do increase with the higher dose.

Keywords: Pregnancy, complications, preeclampsia, antiplatelet therapy

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Introduction

One of the major public health concern is Maternal Mortality and in less developed countries it accounts for >99 % of maternal deaths. Hemorrhage, sepsis, hypertension and its complications are common causes of direct maternal deaths.[1] Maternal Mortality Rate is 276 per 100,000 live births in Pakistan.[2] Deaths due to pre-eclampsia/eclampsia represent one-third of maternal deaths reported at the settings of tertiary care hospitals in Pakistan.[1] Around 2–10% of pregnant women are affected by preeclampsia and makes it a major cause of maternal and perinatal morbidity and mortality. For prevention of preeclampsia, various interventions like frequent antenatal visits, change in lifestyle, nutritional supplementation, and drugs have been studied.[3]

In the prevention of preeclampsia and its complications, the effect of antiplatelet agents has been established, regardless of whether the treatment is started before or after 12 weeks of gestation. Antiplatelet therapy prophylaxis should be considered in women who are at an increased risk of preeclampsia. The frequency of preeclampsia was reduced to 10.7% with antiplatelet therapy in high risk females in one study.[4] Another study showed that frequency of preeclampsia was 8.85% with antiplatelet therapy in high risk females.[5]

Preeclampsia developed in 3.7% cases with antiplatelet therapy according to one metaanaysis.[6] A systematic review showed that 16.1% females developed preeclampsia without antiplatelet therapy.[7]

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This study has been conducted to assess the frequency of preeclampsia with higher dose of antiplatelet therapy given before 12 weeks of gestation in high risk females. Literature has ambiguous results regarding efficacy of 120mg antiplatelet therapy. Also there is no proposed local study in this regard. So, this study was conducted to findout the efficacy and side effects of 120mg antiplatelet therapy in high risk females to prevent development of preeclampsia. The results will help to update local guidelines and can also help to change our current practice of pre-eclampsia prophylaxis with 75mg Antiplatelet therapy.

Methods

Study Design: Descriptive case series

Settings: Department of Obstetrics and Gynecology, Sir Ganga Ram Hospital Lahore

Duration of Study: Six months, from November 28, 2018 till May 28, 2019.

Sample Size: Sample size of 200 cases was calculated with 95% confidence level, 4% margin of error and taking expected percentage of preeclampsia i.e 8.85% with antiplatelet therapy in high risk females.[5]

Sampling Technique: Non probability, consecutive sampling.

Sample Selection Criteria

Inclusion criteria: Females of age 20-40 years, parity <5 presenting in gestational age <12 weeks (according to LMP) for antenatal check-up for high risk pregnancy.

Exclusion criteria:

- Females with systemic problems i.e. deranged LFTs (ALT>40IU, AST>40IU, bilirubin> 5IU/L),
- Females deranged RFTs (creatinine>1.2mg/dl).
- Females with cardiac problem (abnormal ECG and medical record)
- Females with existing placenta previa
- Females with fibroid uterus in pregnancy (on ultrasound)

Data Collection Procedure

Total 200 females, fulfilling the selection criteria were recruited in this study from OPD of Department of Obstetrics & Gynecology, Sir Ganga Ram Hospital, Lahore. Informed consent was taken and demographic details(name,age, gestational age, parity and BMI) were recorded. All females were given 120mg/day of antiplatelet therapy (aspirin). All participants were followed-up monthly till 30 weeks and then fortnightly till 36 weeks of gestation for development of high BP, proteinuria or side effects of Aspirin. If female developed BP 140/90mmHg and proteinuria>+1 on dipstick method, then preeclampsia was labeled. All this information was recorded on pre-designed Performa. The females who developed preeclampsia were managed as per hospital protocol. Complications of antiplatelet therapy such as antepartum hemorrhage, acid peptic disease and low platelets were also recorded. Any patient developing any side effects was managed efficiently as per standard protocol.

Data Analysis

Data was entered and analyzed by SPSS version 21. Mean and SD was calculated for age, BMI and gestational age. Frequency and percentage was calculated for pre-eclampsia. Parity was presented as frequency. Data was stratified for age, gestational age, parity type of underlying condition and BMI. Post-stratification, chi-square test was used with P-value 0.05 taken as significant.

Results

The mean age of all participants was 29.87 ± 5.82 years with minimum and maximum age as 20 and 40 years respectively. The mean body mass index was 28.31 ± 2.55 with minimum and maximum BMI as 24 and 33.9kg/m^2 respectively. The mean gestational age was 33.54 ± 3.52 weeks with minimum and maximum gestational age as 28 and 39 weeks respectively. There were 81(40.5%) females who had parity <3 and 119(59.5%) females had parity as 3-4. There were 12(6%) females who had pre-eclampsia in previous pregnancy, there were 45(22.5%) obese cases, there were 16(8%) females who were chronic hypertensive, and 138(69%) females who had gestational hypertension and 37(18.5%) cases who had gestational diabetes. There were 25(12.5%) cases who developed preeclampsia, 94(47%) cases who had antepartum hemorrhage, 64(32%) cases had acid peptic disease and 17(8.5%) cases had low platelets.

The data was stratified for the age of the patient. In age group of 20-30 years, 11.3% of patients developed pre-eclampsia. In age group of 31-40 years 13.8% patients developed preeclampsia. The data was stratified

with respect to parity. In patients with parity<3, 17.3% patients developed preeclampsia and with parity 3-4, 9.2% patients developed preeclampsia. The data was stratified with respect to gestational age. In patients with gestational age 28-34 weeks, 10.8% patients developed preeclampsia, and with gestational age 34.1-39 weeks 14.3% patients developed preeclampsia. Data was stratified with respect to preeclampsia in previous pregnancy 33.3% patients developed preeclampsia and in patients with no history of preeclamsia the percentage was 11.2%. Data was stratified with obesity. In obese patients, the percentage of developing preeclampsia was 15.6% and in non-obese it was 11.6%. Data stratification with respect to chronic hypertension showed the percentage of development of preeclampsia with positive history of chronic hypertension as 0% and with no history as 13.6%.

Discussion

Development of hypertension and proteinuria after 20 weeks of gestation defines pre-eclampsia and is associated with increased risk of long term cardiovascular mortality for mother and infant[12]. The World Health Organization recommends administration of low dose aspirin (75 mg/day) should be started during early pregnancy to prevent preeclampsia in high risk females should[13]. Complications of preeclampsia, for example, perinatal death, preterm birth, and having a small for-gestational-age baby, are all reduced with the administration of anti-platelet agents. Although the benefits associated with antiplatelet agents are modest, they have public health importance, particularly because their safety is reassured, and aspirin is both easily available and cost effective 48. International guidelines recommend that women who are at an increased risk of preeclampsia should be offered aspirin. However, recommendation regarding timings to start the treatment vary ranging from before or at 12 weeks gestation to before 16 or 20 weeks. Whethe to commence treatment earlier in pregnancy has greater benefits, also remains controversial.[14]

Table 1: *Descriptive Statistics of Age(Years), BMI, Gestational Age in Weeks,*

		Age (years)	BMI	Gestational age(weeks)
Age (years)	n	200	200	200
	Mean	29.87	28.99	33.54
	SD	5.82	2.71	3.52
	Range	20.00	10.00	11
	Minimum	20.00	24.00	28
	Maximum	40.00	34.00	39

Table 2: *Frequency of Preeclampsia and Complications with Antiplatelet Therapy*

	Yes	No	Total
Preeclampsia	25	175	200
Antepartum haemorrhage	94	106	200
Acid peptic disease	64	136	200
Low platelets	17	183	200

Recently a meta-analysis study was conducted and demonstrated that there was significant reduction in overall risk ratio (RR) of preeclampsia regardless of the time of delivery, when compared with placebo or no treatment. It was concluded that when low dose aspirin was commenced at ≤16 weeks of gestation in women at increased risk of preeclampsia was associated with a reduction in overall risk of preterm preeclampsia, and of adverse maternal and neonatal outcomes[15]. Another meta-analysis concluded that there was no significant difference in the effects of antiplatelet therapy for women randomized before 16 weeks gestation compared with those randomized at or after 16 weeks. Antiplatelet therapy should be offered to women at increased risk of preeclampsia, regardless of whether they are first seen before or after 16 weeks gestation.[9]

Another study results showed the effect of aspirin dosage on the prevention of preeclampsia, severe preeclampsia, and fetal growth restriction. They reported that aspirin initiated at >16 weeks was not associated with reduce risk or a dose-response effect for severe preeclampsia and fetal growth restriction. There is no or modest effect on the risk of preeclampsia, severe preeclampsia, and fetal growth restriction when low dose aspirin was initiated at >16weeks. Women who are at high risk for those outcomes should be identified in early pregnancy.[10]

In another study, early vs late administration of lowdose aspirin was compared on the risk of perinatal death and adverse perinatal outcome. When compared with controls, lowdose aspirin started at 16 weeks gestation compared with lowdose aspirin started at >16 weeks gestation was associated with a greater reduction of perinatal death, preeclampsia, severe preeclampsia, fetal growth restriction and preterm birth. So, the study has concluded that Lowdose aspirin initiated at 16 weeks of gestation is associated with a greater reduction of perinatal death and other adverse perinatal outcomes than when initiated at >16 weeks.[11]

Conclusion

It is concluded that the frequency of preeclampsia was very low among high risk females after having antiplatelet therapy in first trimester. Hence, in future by adding antiplatelet therapy in such females presenting with underlying conditions may be prevented from preeclampsia. After reducing the incidence of preeclampsia we may have better fetal and maternal outcome.

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Authors Contribution

S I M, B S, S A: Conceptualization of Project, Literature Search, Drafting, Revision

S A, B S: Data Collection, Statistical Analysis, Writing of Manuscript

Esculapio - Journal of Services Institute of Medical Sciences

Original Article

Evaluation of Glottic Visualization & Ease of Intubation at Induction of General Anesthesia: Comparison Between Macintosh & Mc-coy Blade Laryngoscopes

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Abstract

Objective: To compare the frequency of better glottic visualization and ease of tracheal intubation with Macintosh and McCoy blades.

Methods: This randomized controlled trial was conducted in the Department of Anesthesia, Mayo Hospital, Lahore from September 2017 to March 2018. A total of 60 patients booked for elective surgical procedures under general anesthesia of age ranges from 20-40 years, of both genders, were included. Patients with anticipated difficult intubation, diabetes mellitus, hypertension, pulmonary diseases, and ischemic heart diseases were excluded. Patients were randomly divided in two groups: Group 1 (Mc-Coy) and Group 2 (Macintosh) with 30 patients in each group. Laryngoscopy was performed using McCoy blade in Group 1 and with Macintosh blade in Group 2 and the best possible view of the glottis was sought. Two trained anesthesiologists were involved to grade the view of glottis visualization and ease of intubation.

Results: The mean age of patients in Group 1 and Group 2 was 29.80 ± 6.07 years and 31.93 ± 5.99 years respectively. Out of these 60 patients, 35 (58.33%) were male and 25 (41.67%) were females with male to female ratio of ratio of 1.4:1. Better glottic visualization was found in 60.0% of cases with Macintosh blade and in 83.33% of cases with Mc-Coy blade (p-value = 0.045) and ease of intubation was 73.33% and 93.33% with Macintosh and with McCoy blade respectively (p-value = 0.038).

Conclusion: This study concluded that frequency of better glottic visualization and ease of tracheal intubation with McCoy blades is higher as compared to Macintosh blade.

Keywords: Endotracheal tube placement, glottic visualization, McCoy blades.

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Introduction

Endotracheal intubation is done for various purposes, most commonly for securing and maintaining the airway and ventilation for the conduct of surgery under general anesthesia. Other indications include mechanical ventilation of critically ill patients, securing airway, resuscitation, and to achieve hyperventilation for lowering raised intracranial pressure[1]. Intubation is normally facilitated by sedating or anaesthetizing the patient first and then by the use of some intubation gadget including a conventional laryngoscope, flexible fiberoptic bronchoscope or video laryngoscope to name a few.[2]

Direct view of the larynx using laryngoscopes of various designs has been the corner stone of endotracheal intubation since the advent of artificial ventilation of patients during general anesthesia. Direct laryngoscopy brings the various structures of upper airway including the pharynx and the larynx in one line, thereby facili-tating the process of intubation. However, cases of difficult intubations have always been there, prompting the anesthesiologists to use various sizes and designs of laryngoscope blades to aid in the process.[3,4]

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The popularity of Macintosh laryngoscope in the world of anesthesia is beyond any doubt. Designed by Sir Robert Macintosh, Professor of Anesthesia at University of Oxford, it has revolutionized the conduct of intubation in anesthesia. In 1940s, when the use of straight Miller blade was common and many Anesthetics were struggling with the intubations particularly due to lack of the discovery of muscle relaxants, Macintosh designed a curved blade laryngoscope and suggested to place its tip in the valecullae, thus lifting the epiglottis and improving the view for intubation. The ease of intubation with this device made it popular over a quick span of time. Macintosh laryngoscope is still regarded by most of the anesthetists as an easier to master device and a gold standard for intubation even though larynx cannot be viewed properly in 1-3% of the cases by its use.[5]

The McCoy blade of the laryngoscope is a modification in the design of Macintosh blade. The tip of the blade is made hinged which bends by pressing the lever at the handle of the laryngoscope. This further lifts the epiglottis making the device particularly useful for improving the glottic view.[6]

Studies comparing the use of various blades of laryngoscope for the ease of intubation have shown variable results. Kulkerni et al compared the ease of intubation using Miller, McCoy, Macintosh and Trueview laryngoscopes. The ease of intubation was not statistically difference between McCoy blade, Trueview, and Macintosh blade (grade 1 view=93% with McCoy and Trueview and 90% with Macintosh blade). However, statistically significant difference was seen between McCoy and Miller blade with grade 1 view seen in only 57% of patients in Miller group. Barak et al compared the Truview with Macintosh blade. They concluded that Truview provides better laryngoscopic view as compared to Macintosh blade (grade 1 view = 86% and 45% respectively, p value = 0.001).[7,8] We, therefore, planned to compare the Macintosh and McCoy blades laryngoscope for glottic visualization and ease of tracheal intubation in our general population to get further evidence.

Methods

This Randomized Controlled Trial was conducted in the Department of Anesthesia, Mayo Hospital, Lahore from September 2017 to March 2018. After taking ethical approval from the hospital committee and research department, sample size of 60 patients was calculated. The patients were randomly divided into two groups: Group 1 (McCoy group) and Group 2 (Macintosh group), each comprising of 30 patients. Patients of both genders scheduled for elective procedures under general anesthesia, belonging to American Society of Anesthesio-logist physical class 1 and 2 and ranging between 20 to 40 years of age were included in the study. Patients with anticipated difficult intubation on history and physical examination, having diabetes mellitus, hypertension, chronic obstructive airway disease, ischemic heart disease, undergoing head and neck surgery or Body mass index (BMI) more than 30 were excluded. Informed consent for participation in the study was taken from each patient. Randomization was performed using the lottery method technique. Patients in both groups were fasted for solids for at least 6 hours before surgery. Tablet Alprazolam 0.25 mg was given per oral at night before surgery. After application of all the monitoring equipment to the patients, anesthesia was induced with injection Propofol 2-3 mg/kg till the loss of verbal response and maintained with isoflurane in 70% air and 30% oxygen. Loading dose of injection Atracurium (0.4-0.5mg/kg) was injected intravenously to attain adequate muscle relaxation. Injection nalbuphine was given was for analgesia to each patient in a dose of 0.10 - 0.15mg/kg. Assisted ventilation was provided to each patient for four minutes to allow adequate muscle relaxation. Then, laryngoscopy was carried out using McCoy blade in patients belonging to Group 1 and Macintosh blade in patients belonging to Group 2. Two trained anesthesiologists were then asked to report the vocal cord visualization according to Cormark-Lehabe scoring system[9] (Grade-I and 2a as better view, grade 2b to IV as difficult view). Ease of tracheal intubation was determined using Intubation Difficulty Scale (IDS).[10] Score of 0 to 5 was taken as easy to intubate while a score of 6 or more was taken as difficult to intubate. The patients were then intubated using endotracheal tubes of appropriate sizes, cuffs of the tubes were inflated, laryngoscope blade removed, breathing circuits were attached and mechanical ventilation was ensued. Bilateral chest auscultation and capnography was used to ensure the proper placement of endotracheal tubes. All the data including the patients' demographics and findings at the laryngoscopy was recorded on especially designed proforma.

Data was analyzed using SPSS version 20. Frequency and percentage were calculated for qualitative variables like gender, ASA score, glottic view and ease of tracheal intubation. Mean±SD were calculated for quantitative variables like age, weight, and BMI. Chi-square test was applied to compare glottic view and ease of tracheal intubation in both groups. p value of ≤ 0.05 taken as significant.

Results

Patients in both groups were comparable in terms of age, gender distribution, ASA physical class status, weight, and BMI (table-1) with insignificant p values. In our study, we have found significantly better glottic visualization and ease of intubation with McCoy laryngoscope blade as compared to Macintosh laryngoscope blade (table-2).

Table 1: *Comparison of Physical Characteristics of Two Study Groups*

Parameter	Group 1 (n=30)			GROUP 2 (n=30)		
AGE in years (mean ± SD)	29.80 ± 6.07			31.93± 5.99		
Gender	**Male**	n=17	56.66%	**Male**	n=18	60%
	Female	n=13	43.33%	**Female**	n=12	40%
ASA CLASS	**I**	n= 12	40%	**I**	n= 14	46.67
	II	n=18	60%	**II**	n=16	53.33
WEIGHT In kg years (mean ± SD)	81.90 ± 9.47			79.13 ± 9.04		
BMI kg/m^2 (mean ± SD)	30.73 ± 2.38			30.23 ± 2.33		

Table 2: *Comparison of Glottic Visualization and Ease of Intubation in Two Study Groups*

Parameter		Group 1 (n=30)		Group 2 (n=30)		P value
		No.	%age	No.	%age	
Glottic visualization	Better view	25	83.33	18	60.0	
	Difficult view	05	16.67	12	40.0	**0.045**
Ease of tracheal intubation	Yes	28	93.33	22	73.33	
	No	02	6.67	08	26.67	**0.038**

Discussion

The incidence of difficult tracheal intubation during the conduct of anesthesia has been estimated to be around 8%[11]. Conditions necessitating the restriction of the neck movements as in cases with the fracture of cervical spine or joint deformities where the joints are fused or fibrosed raises this incidence up to 20%.[12] Various methods and tests have been designed for the prediction of difficult airway. However, none of them have proven to be 100% accurate in the prediction.[13,14] This failure of prediction of a limited number of cases regarding the difficulty in intubation brings forward the scenarios of "unanticipated" difficult airways. Literature reveals that 1.5 to 8.5 % of the cases poses unanticipated difficulty in intubation.[15,16] Since the advent of Macintosh laryngoscope, its use has gained immense popularity over a very short span of time. It will not be an exaggeration to state that it has become a "gold standard" in the art of laryngoscopy. Cases in which laryngoscopy with Macintosh blade does not reveal the laryngeal inlet adequately, use of assisting gadgets like stylet or gum elastic bougie become handy.[17,18]

The McCoy blade of laryngoscope is essentially a modification in the design of Macintosh blade where the tip of the blade is made hinged to lift the epiglottis when flexed with a lever. This hinged design lessens the application of force required to lift the epiglottis particularly in cases of limited glottic view.[19,20]

We have conducted this study to compare the frequency of better glottic visualization and ease of tracheal intubation in Macintosh versus McCoy blades. We have found that the glottic visualization is better with the use of McCoy laryngoscope as compared to Macintosh laryngoscope (83.33% vs 60% respectively with p-value=0.045). Ease of intubation with McCoy laryngoscope is 93.33% as compared to 73.33% with Macintosh laryngoscope (p-value = 0.038). Garhwal AM and his associate found in their study that better glottic visualization was 15% with Macintosh and ease of intubation was 38.33%[21]. Study conducted by Kulkarni et al. showed better glottic visualization with McCoy blade as compared to Macintosh blade (77% and 63% respectively) and ease of intubation was 93% with McCoy while with Macintosh blade its 90%7. Uchida et al[22] conducted a study on view of glottis with Macintosh and McCoy blade keeping the necks of the patients in neutral positions. They concluded that the glottic view improves in grade when McCoy blade is used in place of Macintosh blade. The results of their study showed that 72% of the patients in the Macintosh group had grade 3 view on laryngoscopy. However, this view improved to grade 1 or grade 2 when McCoy blade was used in 83% of the patients.

The difficulty faced during endotracheal intubation prior to the invention of Macintosh blade was perhaps

more due to the technique rather than the shape of the blade. The straight blades used previously employed a midline approach where the tongue was kept in the center. This required use of far greater force to obtain the adequate view of laryngeal inlet causing the anesthetists to struggle during direct endotracheal intubation. Professor Macintosh with the invention of curved laryngoscope also emphasized on the technique of laryngoscopy by putting the tip of the laryngoscope blade in the vallecula and displacing the bulk of the tongue onto one side, thereby improving the view of laryngeal inlet.[23] The blade of Macintosh laryngoscope incorporates the bulk of muscle mass of the tongue under its curvature and by displacing the tongue to one side further improvement in the view is obtained with far lesser force being used. McCoy further modified the technique by incorporating the hinged tip to the blade of the laryngoscope. Flexing the tip with lever during laryngoscopy further lifts the epiglottis with far less force, improving the view of glottis and aiding in tracheal intubation. Literature shows that the number of attempts at intubation, difficulty in intubation and trauma to the upper airway is lesser when using McCoy blade for direct laryngoscopy in comparison with Macintosh blade.[24,25] Also the laryngoscopic view is seen to be improved by using McCoy blade in patients with rigid cervical collar on or when utilizing manual in-line stabilization techniques for patients with suspected cervical spine injury.[26,27]

Conclusion

This study concluded that frequency of better glottic visualization and ease of tracheal intubation with McCoy blades is higher as compared to Macintosh blade. So, we recommend that use of McCoy blades should be encouraged for obtaining better view of glottis on direct laryngoscopy n and tracheal intubation. Use of Mc-Coy blade can be particularly handy in the scenario of limited glottic visualization.

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Authors Contribution

A G: Conceptualization of Project, Data CoIIection, Literature Search

M M: Data CoIIection

L R: Statistical Analysis

A G, L R: Drafting, Revision

L R, M: Writing of Manuscript

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Original Article

A Hospital-Based Analysis of Frequency of Various Types of Nail Changes in Psoriasis

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Abstract

Objective: To assess the frequency of nail changes in patients of psoriasis.

Methods: This was a hospital-based cross-sectional study conducted in the Department of Dermatology, Allied/ D.H.Q Hospitals, Faisalabad Medical University over a period of six months. After approval from hospital ethical committee, all the patients of psoriasis with nail changes were enrolled through non-probability consecutive sampling. Detailed cutaneous examination was done. Types of psoriatic nail changes i.e. pitting, onycholysis, oil drop discoloration, subungual hyperkeratosis, leukonychia and splinter haemorrhages were noted. Demographic and clinical data was recorded on a predesigned proforma.

Results: Out of total 125 patients, 90 (72%) were males while 35(28%) were females. Mean age of the patients was 37.58±8.19 years. Frequency of various types of nail changes in psoriasis was recorded as follows: Pitting was seen in 77 (61.6%), Onycholysis in 64 (51.2%), Oil drops in 56 (44.8%), Leukonychia in 48 (38.4%), Subungual Hyperkeratosis in 43 (34.4%) and Splinter haemorrhages in 18 (14.4%) patients.

Conclusion: We concluded Pitting as the commonest change in nails of psoriatic patients followed by Onycholysis, Oil drop discoloration, Leukonychia, Subungual hyperkeratosis and Splinter haemorrhages.

Key words: Frequency, Psoriasis, Types of nail changes

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Introduction

Psoriasis is a frequently encountered chronic skin disease which may involve nails and other organs of the body. The chronic inflammatory process in psoriasis may involve the nail bed or nail matrix leading to typical changes of nail psoriasis.[1] Majority of the patients suffering from psoriasis develop nail changes at some time in their life. The frequency has been reported to be as much as 90%.[2] Involvement of nails in psoriasis has been declared as a definite indicator of activity and severity of the disease. It can also predict development of psoriatic arthritis and inflammatory damage to other organs in future. It has a huge impact on psychological and social life of patients especially as it involves cosmetically visible areas of skin.[3] Nail changes in psoriasis are so diverse that they mimic many other commonly encountered nail disorders. Particularly important among those is Onychomycosis which accounts for almost half of all nail diseases.[4] Studies indicate that the two diseases can sometimes be too difficult to distinguish.[5]

Nail involvement in psoriasis is not affected by gender or race. Association with HLA-C0602 has also been negated. However, psoriatic nail changes have been seen in association with inflammation at the insertion sites of ligaments and tendons leading to enthesitis. Therefore, instead of autoimmunity aberrant immune response involving nail-joint unit has been postulated to be responsible for nail disease.[6] Both classical and atypical changes have been reported in psoriasis. Fingernails due to their quicker growth are more prone to these inflammatory changes. Psoriasis may involve nail bed, nail matrix or both. Studies have indicated Nail pits as the most typical and frequently seen nail change in psoriasis. They are produced due to small psoriatic lesions in nail matrix. Complete involvement

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of nail matrix leads to complete destruction of nail plate. Leukonychia is seen as a white band or line formed due to retention of parakeratosis in nail matrix making it opaque. Splinter hemorrhages represent leakage of blood or blockage of dilated blood vessels in nail bed. Other interesting findings include Salmon patches or Oil drops, which are formed due to psoriasis of nail bed and distal matrix. They appear as brown spots with erythematous borders due to retention of psoriatic plaques under the nail plate. Subungual hyperkeratosis and paronychia are other psoriatic nail lesions frequently observed.[7] Red spots in lunulae have been reported as atypical lesions due to psoriasis involving blood capillaries.[8]

Hence, nail psoriasis can manifest in various ways depending on the involvement of nail unit. Affection of nail matrix produces pits, trachyonychia, Beau's lines, leukonychia and onychomadesis, while disease of nail bed is seen as oil drops, subungual hyperkeratosis, onycholysis and splinter hemorrhages.[9] Diagnosis of nail psoriasis is mainly clinical. Many assessment tools are in use to grade the severity and extent of nail involvement in psoriasis. These include Psoriasis Nail Severity Score (PNSS), Nail Psoriasis Severity Index (NAPSI) and Modified Nail Psoriasis Severity Index (mNAPSI). The mNAPSI scale is considered to be more reliable and objective tool of assessing nail involvement.[10]

Management of psoriatic nail disease is complicated and difficult due to many factors. Most important of these hurdles is the poor penetration of drugs through nail plate. Treatment depends upon the extent and severity of disease, presence of arthritis and patient preferences. Topical agents, cosmetic procedures, biological and non-biological drugs are some of the available treatment options.[11]

Due to the cosmetic issues associated with nail disease in patients of psoriasis, psychosocial morbidity and extremely challenging treatment strategies, the quality of life of patients is negatively impacted upon. Psoriasis is considered as a psychosomatic disorder, which means physical and psychological factors concomitantly are involved in aggravation of disease,[12] therefore this stress can further make the treatment difficult or ineffective.

The purpose of this study was to assess the frequency and pattern of nail changes in psoriasis in our population in order to better understand and formulate the strategies for their management, since clinical data is limited in nail psoriasis in our population. Up to 5% patients may present with nail changes of psoriasis in the absence of cutaneous lesions,[13] in these cases by knowing the pattern of nail disease we may predict and prevent development of skin lesions in future. By knowing the magnitude of the problem, we can play an important role in reducing the anxiety and misery of patients and help them better cope with their appearance and psychosocial issues. This may eventually lead to better management of this psychosomatic disorder.

Methods

After getting approval from Ethical Review Board, patients of nail psoriasis presenting to the Outpatient Department of Dermatology, Allied/ D.H.Q Hospitals, Faisalabad Medical University were enrolled from May 2020 to November 2020. Patients were selected by non-probability consecutive sampling. Inclusion criteria included adult patients from 15 to 55 years of age, who were diagnosed cases of Psoriasis on basis of presence of erythematous, scaly plaques on body and having nail changes of psoriasis. Patients who were excluded from the study were; patients having any other co-existing disease of skin or nails or any systemic illness which may lead to nail changes. Patients suffering from onychomycosis proven by microscopy or culture were also excluded.

After taking written informed consent, patients of nail psoriasis were enrolled in this cross-sectional survey. Their demographic data was registered on predesigned proformas. The pattern and type of nail disease was noted by physical examination

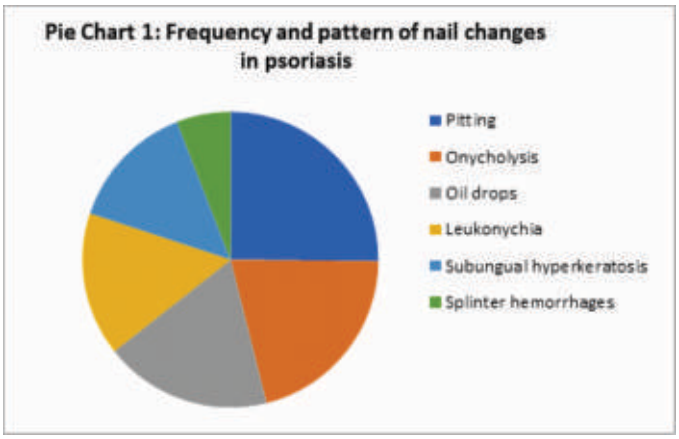
Data was entered and analysed using SPSS Vs 27. Descriptive statistics were calculated for all variables. Mean and standard deviation was calculated for all quantitative variables like age. Frequency and percentages were calculated for qualitative variables like gender and type of disease.

Results

A total of 125 patients were included in the study during the study period of six months. Mean age of the patients was 37.58±8.19 years. It was observed that 28 (22.4%) patients were 15-30 years old, while 97 (77.6%) were between 31-55 years of age. There was significant male predominance in our study, 90 (72%) were males while

remaining 35 patients (28%) were females (Table-1).

Frequency and pattern of various nail changes noted was as follows: Pitting was seen in 77(61.6%), Onycholysis in 64 (51.2%), Oil drops in 56 (44.8%), Leukonychia in 48 (38.4%), Subungual Hyperkeratosis in



43 (34.4%) and Splinter haemorrhages in 18 (14.4%) patients (Pie chart 1).

Table 1: *Descriptive Demographic Data of Patients*

		No. of Patients (n = 125)	
		n	%
Gender	Male	90	72
	Female	35	28
Age	15–30	28	22.4
	31-55	97	77.6
Pattern of nail changes	Pitting	77	61.6
	Onycholysis	64	51.2
	Oil drops	56	44.8
	Leukonychia	48	38.4
	Subungual hyperkeratosis	43	34.4
	Splinter hemorrhages	18	14.4

Discussion

Nail manifestations due to psoriasis are varied. These are mainly divided into those affecting the nail bed (onycholysis, oil drops, subungual hyperkeratosis and splinter hemorrhages) and nail matrix (pitting, Beau's lines, leukonychia, mottled lunulae and onychomadesis).[14]

We found that Nail pitting was the commonest (61.6%) psoriatic nail change seen in our patients (Fig 1), followed by onycholysis, oil drops, leukonychia, subungual hyperkeratosis and splinter hemorrhages (51.2%, 44.8%, 38.4%, 34.4% and 14.4% respectively).

We found that most our patients were males (72%) and rest were females (28%). Other researchers have also reported male preponderance in cases of nail psoriasis. Yap et al[15] studied 520 patients of psoriasis in Malaysian population and concluded that 65.6% of them had nail changes. 61.3% of those with nail changes were males. This was comparable to our results. However, they found Subungual hyperkeratosis as the most frequent (90%) and pitting as the least common (50.4%) nail change in psoriasis. This was contrary to our findings. The mean age of their study population was also higher than ours.

Fig 1: *Pitting of Nails in a 35 Years Old Patient of Psoriasis*

Armesto et al[16] studied pattern of nail psoriasis in 661 Spanish patients. They also found that nail changes were 13.5% more frequently seen in males than females. They reported a frequency of nail psoriasis of 47.4%. They reported higher incidence of nail changes in association with psoriatic arthritis, longer disease duration, higher body mass index and a positive family history. These findings were also supported by Mease et al[17] who reported the incidence of nail changes to be 40.5% with higher incidence and severity in males, those with psoriatic arthritis and higher disease related severity scores. They also highlighted that nail involvement was associated with more pain, fatigue, disability and loss of job than without nail involvement.

Mirza et al[18] surveyed 100 patients of psoriasis in Karachi and reported presence of nail changes in 79% patients and higher prevalence of nail changes in males. They observed ridging of nails as the most frequent (94.93%) nail change due to psoriasis followed by pitting, discoloration, onycholysis, subungual hyper-

keratosis, paronychia, melanonychia and splinter hemorrhages.

Marina et al[19] studied pattern of nail changes in psoriatic patients of Romania and concluded that severity of nail changes correlated with severity and age of onset of cutaneous lesions. Another interesting observation they reported was that third fingernail of right hand and first fingernail of left hand were most severely involved in majority of cases. They too observed pitting to be the most common nail manifestation of psoriasis, followed by oil drops and subungual hyperkeratosis.

In Tunisia, Jendoubi et al[20] studied association of nail psoriasis and onychomycosis. They reported nail changes in 71.2% patients of psoriasis. However, this percentage increased to 90% in patients of psoriatic arthritis. They too documented male predominance as we did. They found subungual hyperkeratosis to be the commonest nail manifestation of psoriasis, followed by onycholysis, pitting and leukonychia. This was contrary to our results probably due to the military and ethnic background of the study population.

In an Iranian study,[21] 69.5% patients of psoriasis had nail changes. Most common abnormality noticed by them was onycholysis, followed by pitting and salmon patches. They too reported higher prevalence of nail changes in patients of psoriatic arthritis.

Psoriasis is a common skin disease with an unknown aetiology and unpredictable course which leads to a particularly huge dilemma especially in darker races like ours where beauty and complexion have conventional standards and enormous psychosocial impact.

In our sociocultural setup, nails form an integral part of physical and cosmetic appearance. Damaged or unsightly nails due to disease process severely damage the psychological wellbeing of the patients. These factors can seriously impair the social life of psoriasis patients especially the females. Since stress has a profound effect on causation and aggravation of diseases like psoriasis and this can lead to difficulty in management of patients. Therefore, for effective management of patients, adequate knowledge of the pattern of nail disease is inevitable.

Conclusion

Nail psoriasis has a significant impact on psychosocial life of patients. Dermatologists should pay more attention towards this aspect of the disease and treat it appropriately with available modalities.

Conflict of Interest: None

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Authors Contribution

AM: Conceptualization of Project
AK: Data Collection
AS: Literature Search
AS: Statistical Analysis
MS: Drafting, Revision
HT: Writing of Manuscript

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Original Article

Association of Lifestyle Factors with Fetuin-A in Adolescents Having Familial Diabetic Background

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Abstract

Objectives: A study was carried out to find the association of lifestyle factors with Fetuin-A in adolescents having familial diabetic background.

Methods: Study was conducted in the department of Biochemistry and department of Pathology from January 2019 to December 2019 at SIMS, SHL. Study included 35 self reported healthy male adolescents of ages 18-19 years having positive familial diabetic background (group A) whereas the subjects of same age and gender without familial diabetic background (relatives of type 2 diabetics) were placed in control group (group B). Type 2 diabetics and subjects having metabolic syndromes other than type 2 diabetes were excluded. Convenient sampling technique was used. A questionnaire based on demographic variables including lifestyle and eating habits was filled by study subjects after their informed consent. Serum levels of fasting blood glucose were estimated by autoanalyzer (HUMAN) and insulin and Fetuin-A by ELISA. Data was analyzed by SPSS 20.

Results: It was observed that 67% of total study subjects were having sedentary lifestyle and using energy dense diet and beverages in routine and found to have relatively higher levels of fasting blood sugar, serum insulin and serum Fetuin-A. However, when two groups were compared, statistically significant increase in levels of serum Fetuin-A was observed in group.

Conclusion: An association was observed between sedentary lifestyle, dietary pattern, and Fetuin-A in adolescents having familial diabetic background (group A).

Key Words: lifestyle factors, Fetuin-A, adolescents having familial diabetic background.

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Introduction

Type 2 diabetes mellitus is a complex, persistent metabolic problem. It displays a heterogeneous etiology with genetic predisposition and environmental factors which are important causes for expression of disease. It is diagnosed more frequently in children and adolescents.[1] Type 2 diabetes in adolescents is termed as early onset adult type 2 diabetes mellitus. The incidence of early onset adult type 2 diabetes mellitus was 15 to 20 % globally.[2]

Concept of early-onset adult type 2 diabetes is supported by different factors like phenotype, unhealthy diet, sedentary lifestyle or increased duration of sitting may result in continued hyperglycemia with severe impact leading to overwhelming micro- and macrovascular complications.[4] Although non-genetic factors create a direct link between type 2 diabetes and insulin resistance, the heritability also displays the arousal of type 2 diabetes mellitus from beta-cell dysfunction.[5]

Environmental and sedentary lifestyle are generally thought to increase the risk and incidence of early onset type 2 diabetes mellitus worldwide in current decades. Research based on physical inactivity with a concept that most of the time, individuals are sitting whether for their kind of job or watching television that

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may affect the health with resultant poor metabolism of glucose & lipids leading to increased risk of diabetes mellitus, cardiovascular problems.[6] Sedentary lifestyle not only affects above mentioned metabolic pathways but it may also increase the level of serum Fetuin-A and reduce the sensitivity of insulin.[7]

Fetuin-A is a glycoprotein mainly produced by liver and powerfully related to parameters associated with dysregulation of metabolic homeostasis like sensitivity of insulin, tolerance of glucose and levels of lipid profile. Fasting insulin level in non-diabetics must be < 25 mIU/L.

Besides, Fetuin A directly increases the insulin resistance (0.5-1.4) via blocking the action of insulin, decreasing glucose transporter GLUT-4 sensitivity and inactivation of insulin receptor tyrosine kinase in liver and muscles. Additionally, it also interferes with the action of insulin in adipocytes.[8] It is proposed by studies that regular exercise reduces Fetuin-A secretion from the liver and improves liver related insulin sensitivity in metabolic diseases including diabetes.[9]

Sedentary behaviour has appeared as a public health problem and increases the risk of non-communicable diseases. Globally, education, transport and relaxation time progressively shift many forms of physical activity into sedentary lifestyle. Now a days, individuals of every age group spend 50 % of their waking day in sitting that need small expenditure of energy. High levels of sedentary behaviour are related to high risk of non-communicable diseases including diabetes. It is therefore need of hour to find the parameters which may prove to be a link between sedentary lifestyle and risk of diabetes especially in adolescents who have a familial diabetic background.

Current study was aimed to determine the association of lifestyle factors with Fetuin-A in adolescents having familial diabetic background

Methods

A comparative cross-sectional study included 35 male adolescents of 18-19 years of age with risk factor as group A. Thirty-five subjects of same age and gender without risk factor were taken as group B. Both adolescents with and without familial diabetic background (Relatives of type 2 diabetics) were taken from diabetes management center of Services Hospital, Lahore. Study duration was January 2019 to December 2019. A questionnaire based on demographic variables was filled by study subjects after their informed consent. Ethical approval of study was given by IRB committee of Services Hospital, Lahore.

About 5.0 cc blood was drawn from study subjects of both groups in fasting condition for estimation of blood glucose, serum insulin and serum Fetuin-A. Fasting blood glucose was estimated by glucose oxidase method using Auto analyzer (HUMAN). Level of serum insulin and Fetuin-A was analyzed by the technique of ELISA. Insulin resistance was calculated by formula: fasting insulin (micro-U/L) x fasting glucose (n mol/L)/ 22.5.10

Data of both groups was entered and analyzed by SPSS 20. Quantitative parameters age, BMI, biochemical parameters were expressed as mean ± SD. Independent student 't' test was used to compare the age, BMI and biochemical parameters of group A and group B. p-value < 0.05 was considered as a statistically significant value.

Results

Demographic variables in male adolescents (first degree

Table 1: *Demographic Variables in Study Subjects (Group A and B)*

Variables	Male adolescents (n=70)
Age (years)	19.7±2.27
BMI (Kg/m^2)	24.94±1.66
Lifestyle	Sedentary(67 %) Active(33%)
Socioeconomic status	Upper class (65%) Middle class (35%)
Dietary Pattern	Balanced diet (30 %) Junk food (70%)
Current residence status	Day scholar (36 %) Hostellers(64 %)

Table 2: *Variation in the Level of Fasting Blood Sugar, Serum Insulin and Serum Fetuin-A in group A and Group B. Values are Expressed as Mean ± SD*

	Male adolescents With familial diabetic background (35)	Male adolescents without familial diabetic background (35)
Fasting blood sugar(mg/dl)	93.51±7.36	87.23±7.37
Serum Insulin(mIU/L)	5.99±2.3	5.85±3.61
Serum Fetuin-A(mg/l)	195.17±188.16*	157.26±138.82
Insulin resistance	0.99	0.76

*P < 0.05= Significant difference

relatives of diabetics) showed that mean age of adolescents was 19 years with a BMI 24.94 Kg/m^2. In 67% of study subjects, the lifestyle was sedentary while 33% were active. 65% belonged to upper socioeconomic class while 35% belonged to middle socioeconomic class. 30% were consuming balanced diet whereas 70% were consuming junk food as a major portion of their diet. 64% were living in hostels while 36% were day scholars. (Table 1). Variation in the level of fasting blood sugar, serum insulin and serum Fetuin-A in male adolescents with and without familial diabetic background was observed. Levels of fasting blood sugar, serum insulin and serum Fetuin-A were increased in group A as compared to group B. Values of insulin resistance were increased in male adolescents with familial diabetic background. Statistically significant difference was only observed in case of serum Fetuin-A. (Table 2).

Discussion

The incidence of type 2 diabetes in young male adults is noticeably increasing with risk factors of sedentary lifestyle independent of BMI. [11]

We found that majority of male adolescents have sedentary lifestyle and raised values of Fetuin-A (marker of insulin resistance). Number of studies reported sedentary lifestyle in adolescents as well as other age groups and demonstrated that more sitting time seems to be related with diabetes independent of BMI. A study was carried out on 800 healthy individuals having sedentary lifestyle. Study observed that their sedentary time was indirectly related with sensitivity of insulin[12]. Another study found that sedentary time was considerably associated with raised blood glucose, insulin secretion, insulin resistance, Fetuin A and lipid profile and may increase the risk of type 2 diabetes.[13]

It is proposed that skeletal muscle may have a role in homeostasis of glucose and insulin resistance. Study based on the role of exercise or physical activity in increasing the uptake of glucose on skeletal muscle gives insight on auxiliary materials that mimic the adaptations of skeletal muscle to exercise.[16] Contrariwise a study found that insulin-secretary ability is reduced in first degree relatives of diabetics in comparison to their controls. However, the maximal glucose uptake rates are similar in both experimental and control groups who have regular exercise.[14]

Impaired expression of diabetes related gene is also observed with changing the phases of active lifestyle into inactive lifestyle. It is noticed that immobility motivates the expression of many genes and represses the expression of many genes and may affect metabolic pathways.[15] We observed an inverse association between Fetuin-A and active lifestyle in adolescents having familial diabetic background. Some studies also found that Fetuin-A is a biomarker to evaluate the physiological reaction to physical inactivity. It is demonstrated that Fetuin-A is an early predictor of insulin resistance which have major role in progression of type 2 diabetes. Insulin resistance arises due to combined effect of genetic predisposition and lifestyle factors including lack of physical exercise and unbalanced nutritional habits. Exercise can stimulate molecular signaling path-ways which can interfere with glucose uptake.[16] Results of a recent study showed the quantity of Fetuin-A secre-ted by the liver may be a significant determinant of changes in insulin sensitivity of body. Study concluded that Fetuin-A may be a valuable marker of individual disparity due to lifestyle involvements.[7]

We agreed with a study who also found that western diet (junk food and beverages):an energy dense diet in conjunction with a sedentary lifestyle is the primary cause of type 2 diabetes. Study also found that there is a high risk of damage to β-cells in those individuals who have familial diabetic background. As loss of function of β-cells is the definitive reason of developing type 2 diabetes.[17] Additionally beverages (sugar-sweetened) constantly seem to promote diabetes risk.[18] We also found that most of the subjects were living in hostel. It is now common majority of subjects are living alone or living without family as they came from different cities. A study also stated that most of males not females are living solitary life which may be related to increased threat of type 2 diabetes.[19]

Conclusion

An association was observed between sedentary lifestyle, dietary pattern and Fetuin-A in adolescents with familial diabetic background. It is therefore a need of schemes for promotion of active lifestyle with activities based on aerobic fitness which may prevent the adolescents from prediabetic lifestyle and associated environmental factors. However, more research is needed on schemes used for the protection from type 2 diabetes mellitus.

Conflict of Interest: None

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Authors Contribution

N S, T F K, R K: Conceptualization of Project
N S: Data Collection
N S, M S, R K: Literature Search
R A, I A, M S: Statistical Analysis
T F K, I A, R A: Drafting, Revision
N S: Writing of Manuscript

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Original Article

Hepatoprotective & other hepatic histopathological effects of Cinnamon, Pyridoxine and Pitavastatin in Treating High-Fat Diet-Induced Murine Dyslipidemia

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Abstract

Objective: To look for hepatic histopathological & hepatoprotective effects of pyridoxine, pitavastatin & cinnamon in diet-induced dyslipidemic rats.

Methods: 10 groups (60 albino male rats, age: 6 weeks) were included (Group 1: control). Group 2 (dietary preventive) and Groups 3-10 (therapeutic) were induced using HFD for 30 days (HFD continued throughout). They were treated for 30 days, after induction, orally, once a day with pitavastatin (PIT), aqueous cinnamon extract (ACCE) and pyridoxine (PYR) in various combinations: Group 3 (Pitavastatin 0.3mg/kg); Group 4 (Pyridoxine 18mg/kg), Group 5 (ACCE 200mg/kg), Group 6 (Pitavastatin 0.3mg/kg + Pyridoxine 18mg/kg), Group 7 (Pyridoxine 18mg/kg + ACCE 200mg/kg), Group 8 (Pitavastatin 0.3mg/kg + ACCE 200mg/kg), Group 9 (Pitavastatin 0.3mg/kg + Pyridoxine 18mg/kg + ACCE 200mg/kg) and Group 10 (Pitavastatin 0.15 mg/kg + Pyridoxine 9mg/kg + ACCE 100mg/kg). Animals were sacrificed (Day 60); slides were prepared for histopathology from livers (architectural distortion, epithelial damage, inflammation, fatty change, cytoplasmic changes, Kupffer cell hyperplasia). SPSS 20.0 ($P \leq 0.05$) was used to analyze data.

Results: Livers of rats in groups treated with pyridoxine and cinnamon (Group 4, 5 & 7) remained unaffected. Rats in groups 3, 6 & 10 showed mild while combination groups (8, 9) showed mild to moderate fatty change (46.7% rats) and inflammation (46.7% rats). 8 (13.3%) rats showed distorted architecture.

Conclusion: Cinnamon and pyridoxine can be "safer" alternatives to standard dyslipidemia treatment, either alone or in different combinations with pitavastatin.

Keywords: Pitavastatin, Pyridoxine, Cinnamon, Dyslipidemia

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Introduction

Dyslipidemia, a recent term coined for hyperlipidemia, refers to elevated levels of plasma lipids & disturbance in metabolism of various lipoproteins[1]. Dyslipidemia if persists, can prove to be quite harmful (with high risk of developing cardiovascular diseases) and can give rise to various complications[2]. If the control is not achieved, pharmacotherapy becomes necessary to reduce the risk of complications by 30% in 5-years.[3] Dyslipidemia can lead to changes in hepatic histo-architecture. It can lead to fatty inclusions causing fatty liver, inflammatory changes, fibrosis, distortion of hepatic architecture and development of hepatic tumors and cancers. Excessive fatty acids can result in lipid-induced toxicity (lipotoxicity)-induced steatosis and hepatic dysfunction. [4]

Because of their effectiveness, statins have been commonly used for the pharmacotherapy of dyslipidemia. Pitavastatin, like other statins, is HMG (3-hydroxy-3-methyglutaryl) CoA-Reductase inhibitor which inhibits hepatic cholesterol biosynthesis. It lowers the total cholesterol and LDL-C and also raise HDL slightly. Pitavastatin enhances the LDL receptor expression and assembly in liver, hence, increasing LDL-C extraction from the blood. Pitavastatin has a

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highly liver-selective distribution due to carrier-mediated uptake and an extensive first-pass hepatic extraction[5].
Pitavastatin and other statins are generally safe and not toxic.[6] However, an issue of poor compliance and discontinuation of therapy can be there because statins (in high-doses) may lead to some adverse effects. Adverse effects may include raised liver enzymes, hepatotoxicity, myopathy, teratogenicity, cognitive dysfunction on prolonged use, impaired glucose control and drug-drug interactions (DDIs) due to cytochrome enzyme inhibition.[7] Hepatotoxicity from statins can range elevated liver enzymes to hepatic failure but serious injury is very rare and is mostly seen in underlying liver disease or alcoholism.[7] Statins are generally safe and well-tolerated. Their wide-spread use has a positive effect on the global burden of cardiovascular diseases. They are believed to protect the liver from dyslipidemia-induced damage and actually play a hepatoprotective role there.[8] Others advocate absence of hepatic adverse effects in mice treated with pitavastatin and protect against lipid-induced hepatocellular tumors. Moreover, pitavastatin, out of all other statins is superior in terms of safety because it is less involved in drug interactions.[9]
Use of phyto-products is gaining importance, as people are reverting to more natural choices. Drugs can become difficult to consume due to non-compliance: fear of adverse effects or effects themselves, issues with affordability, etc. Many plants and herbs are making a comeback e.g. for dyslipidemia and cardio-protection, dates, ginger, fax seeds, lemon grass and cinnamon are notable.
About cinnamon, it has been postulated that it significantly reduces lipid levels by inhibiting HMG-CoA reductase activity like statins. It may also activate the insulin receptor and launch the insulin cascade system to lower the lipid burden.[10] Some experiments link its lipid-lowering effect to PPAR-γ and PPAR-α activation[11]. It protects against lipotoxic effects on liver. It has been found to be free of adverse hepatic effects especially when used alone.[12] It has anti-inflammatory properties and is found to be hepatoprotective.[13,14]
Several micronutrients have also been found useful for definitive treatment of dyslipidemia e.g. pyridoxine.[10] Pyridoxine (Vitamin-B6) is believed to act in the cholesterol biosynthesis. It may be involved in defense mechanisms against lipid peroxidation in tissues because its deficiency accelerates the process and produces mild dyslipidemia.[15,16] So, its deficiency affects lipid metabolism, modifies the fatty acid composition of some tissues and increases triglycerides and other lipids. As a vital micronutrient, it is generally safe: free of adverse hepatic histopathological effects.
Various combinations of pharmacological drugs e.g., statins and fibrates, fibrates and niacin, etc. are often required to achieve maximum possible control of dyslipidemia in clinical settings, but their combinations can exaggerate adverse muscular and hepatic histopathological effects. Here, in this study, we are experimenting with a safer statin i.e., pitavastatin, hepatoprotective cinnamon and a friendly vitamin, pyridoxine; on diet-induced dyslipidemic rats.

Methods

25mg Pyridoxine and 2mg Pitavastatin tablets were purchased from Clinix Pharmacy, Lahore. Cinnamomum cassia bark was purchased from Hamdard Dawakhana, Lahore. Cinnamomum cassia bark (aqueous) extract was made at UHS, Lahore.
Cinnamomum cassia bark (1kg) was cleaned and shade-dried, extracted, twice, with 4L of distilled water at 90°C for 16 hours. Extract was filtered and freeze-dried for storage at room temperature. It was to be used after being diluted in normal saline (0.9%) and orally administered at 200mg/kg. Dry yield was 8% (w/w).[17] 60 healthy young male albino rats of 6 weeks of age (weight: 150-170 g), were purchased from UHS, Lahore. Rats were kept under standard housing conditions (maintained throughout) in Animal House, UHS. Female, diseased, under-aged and already overweight rats were excluded from the study. Study duration was 60 days.
Groups distribution: Group 2 (dietary preventive group) had High-Fat Diet intake for only 30 days (later on reverted to standard diet till Day 60) and were studied for vital preventive role of "dietary modification" on dyslipidemia. Groups 3-10 were continued to be fed HFD throughout 60 days. University of Veterinary and Animal Sciences, Lahore provided the HFD for the study. 10 groups of 6 animals each (total 60 rats) were used in this study (Table 1).
HFD administered for dyslipidemia induction consisted of: Casein - 120g, Corn starch - 549.6g; Soybean oil - 250g; Cholesterol - 10g, Choline - 0.4g; Salt mixture - 50; Vitamin mixture – 10g and Cellulose – 10g. Total calories (Kcal)/1000g of diet were 5018.4 which was 1000Kcal/1000g greater than normal control diet.[18]
After consumption of HFD and treatment with drugs for 30 days, rats were sacrificed (Figure 1). The livers were removed and fixed in 10% formalin solution to be preserved for histo-architectural studies. From paraffinized tissue blocks, 4µm thick slices were prepared & stained with hematoxylin and eosin.
Slides were prepared at Histopathology Laboratory, Department of Histopathology, Postgraduate Medical Institute, Lahore. They were studied and reviewed at Histopathology Laboratory, Department of Histopathology, Shaikh Zayed Hospital, Lahore. Images were taken at Histopathology Department, Shalimar Hospital, Lahore. Pearson Chi-square test was applied on histopatholo-gical parameters (magnification: 40x).

Table 1: *Groups Details*

Groups	Group Details (Diet & Treatment)
Group 1	Control
Group 2	Preventive Model (HFD + standard diet)
Group 3	HFD + 0.3mg/kg Pitavastatin
Group 4	HFD + 18mg/kg Pyridoxine
Group 5	HFD + 200mg/kg Aqueous Cinnamon Extract – ACCE
Group 6	HFD + 0.3mg/kg Pitvastatin + 18mg/kg Pyridoxine
Group 7	HFD + 18mg/kg Pyridoxine + 200mg/kg ACCE
Group 8	HFD + 0.3mg/kg Pitavastatin + 200mg/kg ACCE
Group 9	HFD + 0.3mg/kg Pitavastatin + 18mg/kg Pyridoxine + 200mg/kg ACCE
Group 10	HFD + 0.15mg/kg Pitavastatin + 9mg/kg Pyridoxine + 100mg/kg ACCE

Results

Hepatic histopathological effects are shown for Group 9 (Figure 1) & Group 10 (Figure 2)

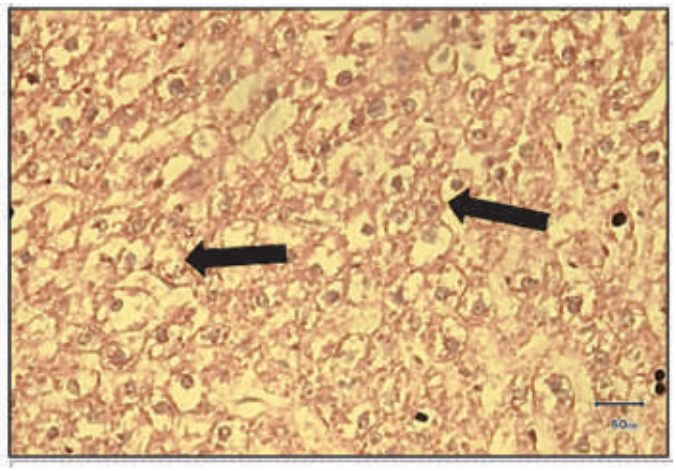

Figure 1: *Group 9 (Pitavastatin 0.3mg/kg + Pyridoxine 18mg/kg+ACCE 200mg/kg) Liver Cross-Section. Archi-tectural Distortion and Epithelial Disruption Seen. Fatty change & Inflammation can also be Seen.*

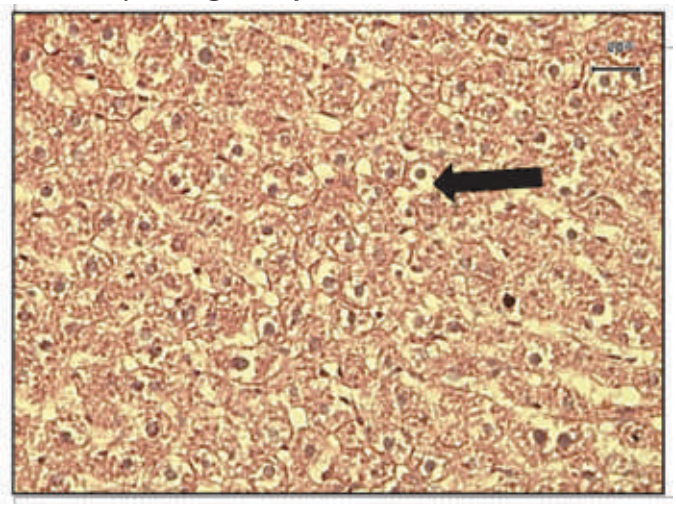

Figure 2: *Group 10 (Pitavastatin 0.15mg/kg + Pyridoxine 9mg/kg + ACCE 100mg/kg) liver cross-section. A: mild steatosis*

Legend:

Group 1: Control
Group 2: high fat diet + no treatment
Group 3: high fat diet + pitavastatin 0.3mg/kg
Group 4: high fat diet + pyridoxine18mg/kg
Group 5: high fat diet + cinnamon 200mg/kg
Group 6: high fat diet + pitavastatin 0.3mg/kg + pyridoxine 18mg/kg
Group 7: high fat diet + pyridoxine18mg/kg + cinnamon 200mg/kg
Group 8: high fat diet + pitavastatin 0.3mg/kg + cinnamon 200mg/kg
Group 9: high fat diet + pitavastatin + pyridoxine + cinnamon (full doses)
Group 10: high fat diet + pitavastatin + pyridoxine + cinnamon (in half doses)
None of the rats showed liver Kupffer cell hyperplasia in the treated or untreated group.

Discussion

The results of hepatic histopathology came out to be favorable (especially combination Group 10
Regarding lobular architecture, 86.7% (52/60) rats belonging to different group, exhibited normal hepatic lobular architecture. Rats in Groups 4 and 5 (pyridoxine and cinnamon, respectively) had normal architecture, highlighting their safety and hepatoprotection. Probable mechanism can be their antioxidant effects. Cinnamon possesses regenerative properties in the liver. Only 8 (13.3%), rats belonging to Groups 2 (preventive), Group 3, Group 8 and Group 9, showed distorted architecture. 13.3% rats with distorted architecture shows generally favorable results. Presence of architecture distortion in 4 out of 6 rats in Group 9 indicates pitavastatin's role in hepatotoxicity.[18,19] The association of treatment with full doses of all 3 treatment drugs with disturbance of hepatic architecture, was significant (P: 0.007).
In untreated Group 2, architecture might have got destroyed due to fatty-diet induced damage. Hepatic damage caused by high-fat diet is due to the deposition of fatty inclusions in form of lipid droplets in the cytoplasm, which join together to push nucleus to side, lead to disruption of architecture and disruption of bile ducts and portal triads: termed as "lipotoxicity"[4]. In other groups, few rats with damaged architecture could also be due to HFD as treatment was only given to all rats for 30 days.
53.33% rats (32/60) did not show any inflammation, including whole Group 4 Group 4 (PYR 18mg/kg) and Group 6 (PIT 0.3mg/kg + PYR 18mg/kg). Findings suggest that oyridoxine has dual actions in treating dyslipidemia: prevention of fat-induced liver inflammation as well as safety against toxic drug effects. The end result of fatty changes in the cytoplasm of the

hepatic cells can lead to inflammation and fibrosis while long-standing liver inflammation can also lead to carcinogenesis & tumorogenesis.

Out of 60, only 46.77% rats (28 rats) displayed mild to moderate inflammation distributed among groups 2, 3, 5, 7, 8, 9 and 10. All the rats of Group 2 and Group 8 showed inflammation in the liver. A strong, significant (P:0.000) association was observed. Hepatic inflammation in (untreated) Group 2 rats shows highlighted severe fatty change (caused by HFD), causing inflammation, fibrosis and hepatic damage. Livers of the rats in Group 8 also showed very mild inflammatory changes which may probably be statin-related.

Pyridoxine, cinnamon and statins, all seem to be hepatoprotective against HFD-induced inflammation & lipotoxicity. Cinnamon and pitavastatin, have significant general anti-inflammatory effects as well. The reported reason for statins' reduction of liver fibrosis in rats is through decrease in the turnover of stellate cells, thus, diminishing the inflammatory response 20. Cinnamon's phytochemical screening (bark) reveals flavonoids, alkaloids, glycosides, tannins, coumarins, anthraquinone, steroids and terpenoids most of which are known to possess hepatoprotection owing to anti-oxidative mechanisms[20,21].

53.33% rats showed exclusive protection from any intensity of hepatic fatty change. Notable among them are Group 4 (PYR 18mg/kg) and Group 6 (PIT 0.3mg/kg + PYR 18mg/kg). However, 46.77% rats exhibited some degree of mild to moderate fatty change. Group 2 (untreated) and Group 9 (all drugs in full doses) showed the most cases of fatty change, probably due to absence of drug treatment. The association was found significant (P: 0.000)

Fat deposition in the hepatocytes can lead to increased lipid peroxidation culminating in damage by free oxygen radicals & development of oxidative stress and mitochondrial dysfunction. All this can lead to hepatic steatosis and steatohepatitis development of which can be favorably retarded with statins 8. Group 9 showed fatty change and the findings were suggestive of 30-day long HFD plus the drug's toxicity (notably statin). But generally statins are safer for considerable periods of time in moderate doses & lead to serious hepatic injury very rarely. So, there should be no serious concerns in terms of prescribing statins.[22] Cinnamon and pyridoxine reduce total hepatic cholesterol content plus slow down and abolish the fatty change because of reduced fat oxidation. Cinnamon also augments fat utilization, upping the overall metabolism.[16]

88.33% rats showed liver specimens with intact epithelia signifying favorable results. 11.7% (7/60) rats distributed among only 3 groups had non-intact epithelia. Group 9 (PIT 0.3mg/kg + PYR 18mg/kg + ACCE) had the most cases, followed by Group 8 (PIT 0.3 mg/kg + ACCE 200mg/kg) and Group 2 (untreated) in order of decreasing frequency.

Aqueous cinnamon extract induces protein synthesis, one of many hepatoprotective mechanisms as it participates in liver cell regeneration[23]. Pitavastatin, as discussed earlier, and pyridoxine, both possess powerful anti-oxidant properties. Anti-oxidant mechanisms help in correcting lipotoxic damage to the cell. The association of the likely causative agent (pitavastatin) with epithelial damage was found significant (P: 0.000). The HFD-induced fatty change and lack of treatment thereof (Group 2) probably caused intracellular fat accumulation leading to disrupting epithelium.

91.7% (55/60) rats showed normal, healthy cytoplasm which signifies that all experimental groups (with exception of Groups 8 and 9) were protected from damage to nuclei and dispersion of nuclear material into cytoplasm. This finding advocates the "hepatoprotection" offered by all these three agents, to varying degrees. Pyridoxine, as suggested by the findings, has been found to be literally free of hepatic adverse effects. In addition, it also augments glutathione activity.

As discussed earlier, cinnamon, like pitavastatin and pyridoxine, retards fat-induced toxicity by anti-oxidant effects. Presence of normal cytoplasm also signifies the positive role of all these agents in providing hepatoprotection. Only a few rats i.e. 8.3% (5) rats belonging to two groups: Groups 8 and Group 9, exhibited acidophilic cytoplasm. The association of the presence of acidophilic cytoplasm with the causative agents (combination of all three drugs in full doses) was significant (P: 0.000).

Kupffer cell hyperplasia was not found to be a positive finding in any group. It vindicates immunological insult to the hepatic tissue, which vouches for the favorability of our three drugs in this case.

Conclusion

The hepatic histopathological effect of treatment of pitavastatin, pyridoxine and aqueous extract of Cinnamomum cassia bark on high-fat diet induced dyslipidemiahave been found fruitful as they have been found to halt the progression of the hepatic damage. It can be deduced from the results that the treatment agents may not only be free of deleterious hepatic effects but also possess "hepatoprotective" potential against high-fat diet-induced hepatic damage. Overall, pitavastatin showed very mild adverse hepatic histopathological effects devoid of any clinical significance. As liver histopathology of untreated dylipidemic rats showed a diverse spectrum of hepatic damage, it is evident that treatment is essential in dyslipidemia. The synergistic effects showed by the combination of all 3 agents (in

half doses) must be investigated further to design beneficial therapeutic combinations with good safety profile.

Conflict of Interest

None

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Author's Contribution

M M.: Conceptualization of Project, Principal Researcher, writing of Manuscript.

S S A.: Supervision of manuscript writing, project

I I: Literature Search

H F: Statistical Analysis, drafting

R T: Drafting, Revision, Data Collection

Esculapio - Journal of Services Institute of Medical Sciences

Original Article

Erythrocyte Sedimentation Rate as A Marker of Prognosis in Patients of Myocardial Infarction

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Abstract

Objective: Frequency of in-hospital mortality of myocardial infarction patients with raised erythrocyte sedimentation rate.

Methods: In this descriptive study, 200 consecutive cases of age 40-60 years with either gender with a definite diagnosis of acute ST-segment elevation myocardial infarction (STEMI) presenting to the medical emergency department were enrolled in the study. ESR sample was taken in all these patients. Data was analyzed in the SPSS version 20.0.

Results: The mean age of patients was 53.01±5.95 years. Out of 200 patients diagnosed with STEMI, 130 (65%) were males while 70 (35%) were female. In patients who died, the mean raised erythrocyte sedimentation rate was found to be 48.47±3.32, while among survival the mean raised erythrocyte sedimentation rate was 45.17±4.12. Mortality was noted in 28 (14%) patients with ST elevation myocardial infarction with raised ESR (>33 mm in 1st hour).

Conclusion: Raised erythrocyte sedimentation rate leads to worse prognosis and increased in-hospital mortality of patients with STEMI.

Key words: Erythrocyte sedimentation rate, Prognosis, Marker, ST elevation myocardial infarction.

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Introduction

Acute myocardial infarction (AMI) or acute coronary syndrome, is a disease in which patients are at a higher risk of long-term cardiovascular mortality and adverse clinical outcome.[1] Chronic inflammatory processes occur as a result of AMI & contributes to pathogenesis and extension of atherosclerosis in acute coronary syndrome.[2] Several inflammatory markers have been studied to predict short- and long-term prognosis of AMI. These include mean platelet volume,[3] platelet-to-lymphocyte ratio,[4] neutrophil count,[5] and C-reactive protein (CRP).[6,7] However prognostic value of the erythrocyte sedimentation rate (ESR) has not been studied that much. Increased ESR in coronary artery disease is useful marker to predict mortality.[8]

ESR is acute phase reactant, very cheap, accurate, and easily available test.[8,9,10] It shows inflammation, infection or malignancy when raised. On the other hand decreased ESR is seen in polycythemia vera. It has also very vital role in the diagnosis of inflammatory as well as in non-inflammatory diseases like acute coronary and syndrome prostate carcinoma.[11] It is of interest that ESR is directly related to atherosclerosis. A small rise in ESR should alert internist and cardiologist to treat coronary artery disease and its possible complications. ESR is an independent predictor of poor outcome & mortality of coronary artery disease.[12]

As ESR is widely available in Pakistan and is routinely used as a nonspecific marker of systemic inflammation, it can be a low cost method to determine prognosis and mortality of STEMI in our population. It has not been studied so far for its prognostic value in ST elevation myocardial infarction in our local population, therefore

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we conducted this study.

Objective

To determine the prognostic value of raised ESR in patients of acute myocardial infarction.

Methods

This was a descriptive study conducted at department of medicine, Mayo Hospital, Lahore for 6 months. 200 patients of ages 40 to 60 years with either gender presenting to emergency department within12 hours of new onset STEMI symptoms who consented to provide blood sample for ESR were included in study. The sample size was calculated by Non probability consecutive sampling by taking 95% confidence, 5% margin of error with expected population proportion of the in-hospital mortality with raised erythrocyte sedimentation rate (ESR > 33mm in 1st hour) in patients with ST-segment elevation myocardial infarction = 9%.[13]

All patients with anemia (Hemoglobin < 10.5 mg/dl), malignancy, connective tissue disorder, end stage renal disease, valvular heart disease, diabetes mellitus and acute or chronic infections were excluded from the study. STEMI was diagnosed by ST-segment elevation of > 1 mm in two or more chest leads or ≥ 2 mm in two or more adjacent limb leads or the presence of new left bundle branch blocks with typical anginal pain for ≥ 20 minutes. Informed consent was taken from all patients. Under aseptic conditions, a venous blood sample was obtained from all patients at the time of admission at medicine emergency department. ESR was measured by Westergren's technique as mm of sedimentation in first hour. Data was collected in structured questionnaire containing background information like age, sex, ESR Level and in-hospital mortality. Data was analyzed by SPSS version 20. Quantitative variables like age and ESR were expressed as Mean ± standard deviation and raised mortality was expressed in frequency and percentage.

Results

The mean age of patients was 53.01±5.95 years. Among two hundred patients, 130 (65%) were females while 70(35%) were males. 52 (26.0%) patients were hypertensive while 148(74%) were non hypertensive. Similarly 40% (80) patients were smokers while 60%(120) were non smokers.

The minimum and maximum elevated ESR noted in the study was 33 and 52 respectively. The mean elevated ESR of the patients was 45.55±4.17. The mean elevated ESR (> 33mm in 1st hour) was found to be higher in males as compare to females (47.31±3.22 vs. 44.6± 4.32). The patients who died in hospital due to MI, their mean raised ESR was found to be 48.47±3.32 while among survivors the mean elevated ESR was 45.17±4.12.

Mortality was noted in 28 patients (14%) of ST Elevation Myocardial Infarction with elevated ESR while 172 patients with raised ESR survived (82%).Out of 200 patients there were 8 patients in ESR range 33-36 mm/hour, 33 patients were in range 37-40 mm/hour, 16 in range 41-44 mm/hour, 80 in range 45-48mm/hour and 63 in ESR range 49-52 mm/hour. Mortality rate was observed to be more common 23(36.5%) in ESR range 49-52 mm/hour while less common (1 and 4 respectively) found in ESR range 37-40 and 45-48 mm/hour. In ESR range 33-36 and 41-44 mm/hour patients no mortality was noted. P value was significant for mortality in raised ESR patients (p=0.001).

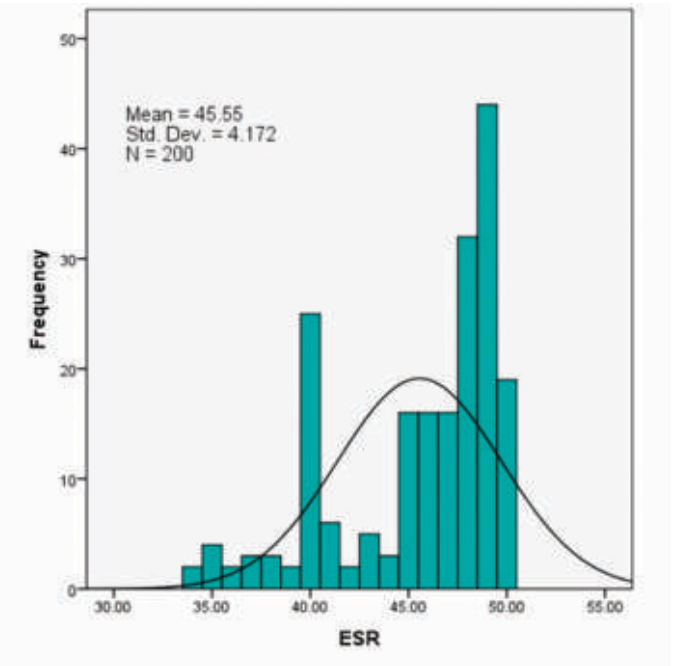

Figure-1: *Graphical Distribution According To The Elevated Erythrocyte Sedimentation Rate In Stemi Patients*

Discussion

In our study it was found that out of 200 patients with raised elevated erythrocyte sedimentation rate (ESR), 28 patients(14%) with ST-segment elevation myocardial infarction died (p=0.001). This shows the significance of ESR as a marker of mortality in MI patients. Our

Table 1: *Descriptive Statistics of the Raised Erythrocyte Sedimentation Rate with Respect to Gender*

Descript.	Gender	N	Mean	Std. Deviation	Std. Error Mean
Raised ESR	Female	130	44.6000	4.32157	.37903
	Male	70	47.3143	3.22824	.38585

Table 2: *Descriptive Statistics of the Raised Erythrocyte Sedimentation Rate With Respect to Mortality*

	Mortality	N	Mean	Std. Deviation	Std. Error Mean
ESR	Yes	28	48.4783	3.32852	.69404
	No	172	44.1695	4.12649	.31017

Table 3: *Descriptive Statistics Of Raised Erythrocyte Sedimentation Rate Groups With Respect To Mortality*

Patients	Esr Range	Mortality		Total	P-value
		Yes	No		
Raised ESR groups	33-36	0	8(100.0%)	8(100.0%)	0.001
	37-40	1(3.0%)	32(97.0%)	33(100.0%)	
	41-44	0	16(100.0%)	16(100.0%)	
	45-48	4(5.0%)	76(95.0%)	80(100.0%)	
	49-52	23(36.5%)	40(63.5%)	63(100.0%)	
Total		28(14.0%)	172(86.0%)	200(100.0%)	

results are well supported by the previous literature.

Fatih OM et al conducted a study to see the impact of ESR on outcome of the patients and found that in-hospital mortality was more common in raised ESR group 14.0% as compare to decreased ESR group 4% as we have seen in our study.[12]

Another study by Lakshmi AB et al scrutinized that in-hospital mortality of patients with raised erythrocyte sedimentation rate in patients with STEMI was noted but was less common (26.6%) among the study groups as seen in our study results.[14]

Erikssen G et al in their study noted that ESR > 30 mm in first hour was observed to be a strong predictor of STEMI mortality after 23 years age and less so for cardiovascular disease mortality, and insignificant for non-cardiovascular disease mortality (25%, 33.3% and 27.8% respectively). Mortality among CAD having STEMI patients was highest in all erythrocyte sedimentation rate (> 30 mm. H-1) as 28/36 (77.8%) as compare to patients of coronary artery disease without STEMI 7/36(19.4%).[9]

In another study Timmer JR et al demonstrated that there was a significant association found between raised ESR and deaths in acute myocardial infarction as 48%. Erikssen G and Timmer JR studies showed high mortality rate due to the increased ESR in patients with AMI occurs via significantly increased RBCs aggregation.[15]

Another study by Farhana S et al found that there is a significant association between raised ESR level and mortality (raised ESR group 26% compared to the lower ESR group 13%). among IHD.[16]

Mehmet FO et al (2012) investigated that raised ESR is associated with worse prognosis in STEMI, concluded that in-hospital mortality rates were significantly higher in patients with raised ESR (9 % vs. 1 %) as seen in our study.[17]

Since the prevalence and prognostic importance of ESR levels in our study was significant, it also necessitate further confirmation and investigation to explain the clinical usefulness of ESR levels to know mortality in STEMI patients.

Conclusion

Prognostic value of ESR in admitted patients (> 33mm in 1st hour) is a cost effective method to predict prognosis and mortality. Present study concluded that high in-hospital mortality is related with raised erythrocyte sedimentation rate (ESR >33mm in 1st hour) in patients with STEMI (14.0%).

Conflict of Interest: None

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Authors Contribution

S M: Data Collection & Analysis, Literature Review, Drafting, Manuscript Writing

F N: Literature Review, Drafting, Manuscript Writing, Revision

S U M: Data Collection, Literature Review, Drafting, Manuscript Writing

T K: Literature Review, Drafting, Manuscript Writing, Analysis

S I: Literature Review, Statistical Analysis, Drafting, Manuscript Writing, Revision

S A: Conceptualization of Topic ,literature Review, Revision, Supervision

Esculapio - Journal of Services Institute of Medical Sciences

Original Article

MR Morphometric Evaluation of Cervical Spinal Canal in Pakistani Population

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Abstract

Objective: To determine the morphometric determinants of cervical spinal canal and spinal cord in Pakistani population and to compare it with other populations and to evaluate gender differences in them.

Methods: This is a retrospective study and included 200 individuals of 19-75 years of age presenting to Radiology department for MRI of cervical spine. MRI study of cervical spine was done. Measurements were taken using sagittal T2 weighted images from C3 to C7 in midsagittal location.

Results: Males had a significantly larger average diameter of vertebral body. The Torg's ratio is higher in females. The average measurements of midsagittal diameter of spinal canal, spinal cord and space available for cord (SAC) did not show any significant gender differences.

Conclusion: It is concluded that MRI is more reliable imaging modality for morphometric analysis of cervical spine than x-rays.

Keywords: Cervical spine, Spinal cord, Torg's ratio.

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Introduction

A large adult population suffers from pain in neck region at some point in life which mostly radiates to upper limbs. In 2015, backache and neck pain were considered 4th among the leading causes of years lived with morbidity. In 2015, it was estimated that more than one third of a billion world population suffers from pain in neck region of greater than three months duration.[1] Stenosis of cervical spinal canal is often the cause. This condition is termed as narrowing of the spinal canal in which lies the spinal cord, its covering layers and nerve roots.[2] The spinal canal size is very important clinically especially in trauma and degeneration. Stenosis of cervical spinal canal is believed to be a predisposing factor for the development of spondylotic myelopathy of cervical region.[3,4]

In 1957, Payne EE and Spillane JD performed a study taking cervical spine lateral radiographs to calculate antero-posterior diameter of cervical spinal canal.[5] Review of literature shows that many studies have been performed on different populations showing variations in spinal canal morphometric values. These variations are largely due to magnification factors associated with plain radiographs apart from genetic and hormonal factors. In order to overcome this problem, Parlov and Torg devised a ratio called as Torg's/ Parlov's ratio to determine spinal canal stenosis. This ratio is calculated by dividing the midsagittal diameter of cervical spinal canal by midsagittal vertebral body diameter.[6,7]

Many imaging modalities are available for evaluating patients presenting with neck pain. Plain radiography is the primary diagnostic modality used to evaluate patients presenting with spinal disease.[8,9] Although plain x rays can very well delineate the osseous structures like vertebral body and spinal canal, but it fails to provide information regarding soft tissues which are also an important contributor to spinal canal stenosis. MRI overcomes this problem as it can accurately measure the spinal canal, as well as spinal cord and also provides information regarding soft tissues. Thus MRI can not only calculate Torg's ratio and other morphometric determinants, but can also calculate space available for cord (SAC) which is determined by subtracting spinal cord diameter from sagittal diameter of spinal canal.[10,11]

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The aim of this study is to determine the morphometric determinants of cervical spinal canal and spinal cord in Pakistani population and to compare it with other populations and to evaluate gender differences in these determinants.

Methods

This is a retrospective study and included 200 individuals (102 males and 98 females) of 19-75 years of age (average age 42.14 ± 12.1 years) who presented to Radiology department for MRI of cervical spine. Patients less than 18 years of age, with infectious, congenital or neoplastic spinal disorders were excluded. MRI study of cervical spine was done on 1.5 Tesla GE MRI machine. The MR protocol consisted of a sagittal T1-weighted fast spin-echo sequence (FSE) (repetition time(TR)/echo time(TE)- 427/10msec; section thickness-3 mm; field of view (FOV)-220 × 220mm; matrix-352×192), sagittal T2-weighted fast recovery fast spin-echo (FRFSE) sequence (3491/109.6; section thickness-3mm; intersection gap-0.5mm; FOV: 220 × 220; matrix 352 × 224), and an axial cube T2-weighted images (1277/92.6; section thickness-1.4 mm; intersection gap-0.7 mm; field of view -200 × 200 mm; matrix 288 × 288). All imaging was performed by a qualified radiographer and evaluated by a consultant radiologist. Measurements were taken using sagittal T2 weighted images from C3 to C7 in midsagittal location. The distances were taken in centimeters.

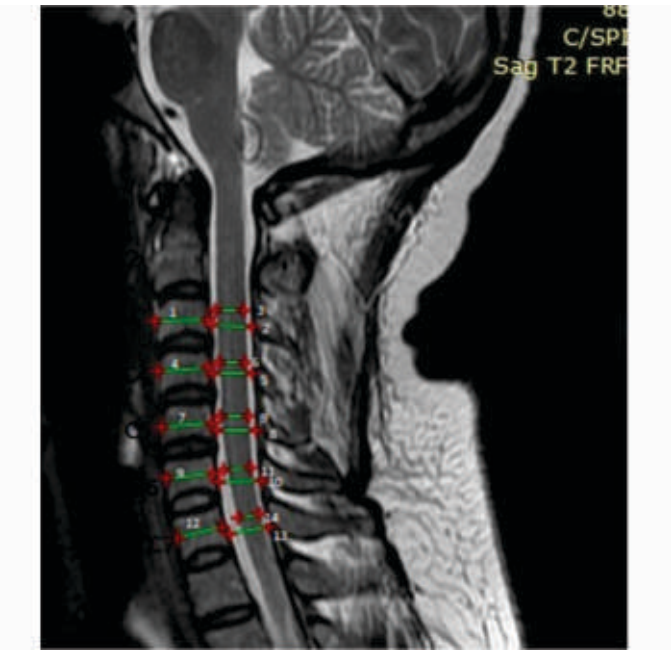

Figure 1: *Midsagittal T2 Weighted Image of Cervical Spinal Cord Showing;*
1, 4, 7, 9, 12: Mid sagittal diameter of vertebral bodies (C3-C7)
2, 5, 8, 10, 13: Mid sagittal diameter of spinal canal (C3-C7)
3, 6, 9, 11, 14: Mid sagittal diameter of spinal cord (C3-C7)

Results

All morphometric determinants were taken from C3-C7 vertebral levels in 200 individuals (102 males and 98 females) of 19-75 years of age (average age 42.14 ± 12.1 years.).

Mid Sagittal Vertebral Bodies Diameter:

Measurements were calculated for both males and females from C3- C7 vertebral levels (table 1). Mean and standard deviation was calculated for both genders. The average sagittal vertebral body diameter was 1.54 ± 0.18 for males and 1.38 ± 0.15 for females. Males had a larger diameter of vertebral body as than females with a p value of 0.043. The maximum average diameter of vertebral body was maximum at C6 vertebral level in both genders.

Midsagittal Spinal Canaldiameter

The midsagittal measurements of spinal canal diameter were taken from C3- C7 vertebral levels for both males and females (table 1). The average cervical spinal canal diameter was 1.16 ± 0.18 for males and 1.16 ± 0.15 for females. There was no statistical difference between the spinal canal diameter for males and females with p value of 0.21. The midsagittal diameter of spinal canal at C4 spinal level was less than measured at C3 spinal level; however it was maximum at C7 spinal level in both genders.

Midsagittal Spinal Cord Diameter:

The measurements were calculated from C3-C7 vertebral levels for both genders and are represented as mean ± standard deviation (table 1). The average cord diameter was 0.69 ± 0.21 for males and 0.66 ± 0.08 for females with no statistical difference between the two genders (p value 0.09). The cord diameter was maximum at C3 vertebral level in females and C4 vertebral levels in males.

Torg's Ratio:

Torg's ratio was calculated by dividing midsagittal spinal canal diameter by midsagittal vertebral body diameter from C3-C7 levels in both genders (table 1). The mean value of Torg's ratio was 0.84 ± 0.19 in males and 0.94 ± 0.19 in females. Females had a statistically higher Torg's ratio than males having a p value of 0.006 due to larger vertebral body diameter in males. (Figure 2,3)

Space Available For Cord (sac):

The values of SAC were calculated from C3-C7 verte-

bral levels for both males and females by subtracting midsagittal spinal cord diameter from midsagittal spinal canal diameter. The mean value of SAC was 0.47± 0.29 for males and 0.50 ± 0.15 for females with no statistically significant difference between the two genders (p value 0.150).

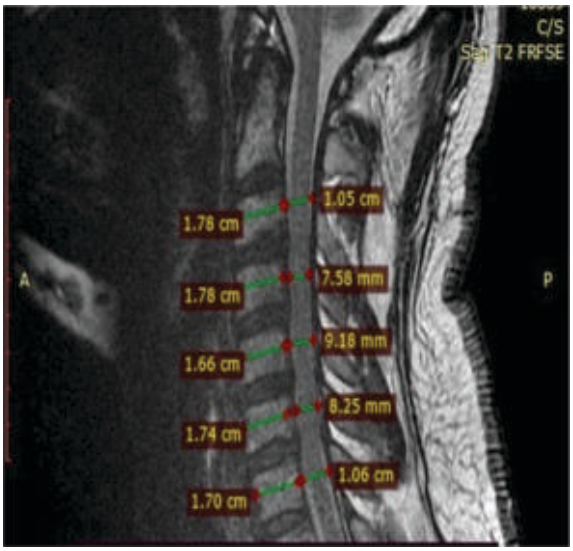

Figure 2: *Torg's Ratio Calculated at C3-C7 Cervical Spinal Level by Dividing Midsagittal Diameter of Cervical Spinal Canal by Midsagittal Vertebral Body Diameter at Each Level.*

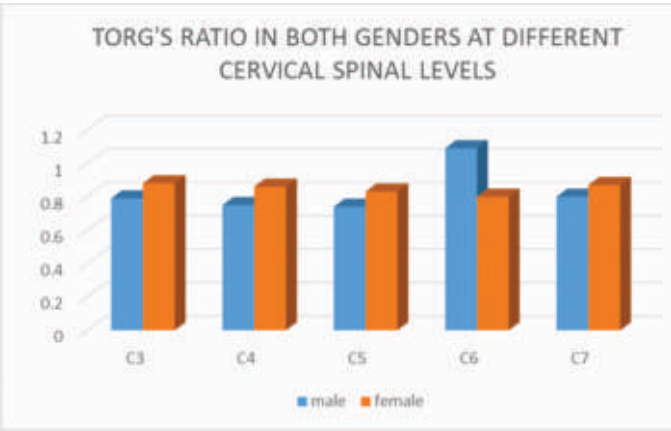

Figure 3: *Torg's Ratio in Both Genders at C3-C7 Cervical Spinal Levels.*

Discussion

Seven vertebrae constitute the cervical spine. The first two cervical vertebra are termed as atypical while C3-C7 comprise the typical cervical vertebra. The cervical spinal canal contains the cervical cord and nerve roots along with investing meninges and CSF. The space available in the spinal canal for spinal cord is essential for free movement of its contents. The size of spinal canal is fairly large in upper cervical region and decreases from C3 till C7. Hence, any condition that decreases the diameter of spinal canal particularly at C3-C7 level will result in abnormal pressure on spinal cord and nerve roots leading to neck pain. Many factors are responsible for variation in the size of the spina canal including mechanical, postural and genetic factors. Therefore it is seen that various studies of spinal canal show variations in different populations. The relationship between cervical spondylotic myelopathy and diameter of spinal canal was established by Payne et al. Many studies have been performed on the morphometry of cervical spine since then. It is seen that there are variation of 1-4mm in in the diameters of cervical vertebral bodies and spinal canal in these studies. These variations can be explained by the fact that many authors have used plain radiography to calculate these measurements. These variations can be attributed to radiographic and patient factors e.g. patient, build, focus to film distance (FFD) etc.[12] Therefore, in recent years MRI is most widely used for morphometric analysis to avoid such discrepancies.

Torg ratio was devised by Torg and Parlov in an attempt to eliminate the discrepancies occurring due to radiographic and subject factors, since the spinal canal and vertebral body diameter on plain radiographs are affected equally by magnification. Moreover it is independent of radiographic and subject factors like FFD and patient build etc. They proposed that a Torg's ratio <0.8 suggests

Table 1: *Mid sagittal diameters (MSD) of vertebral bodies, spinal canal, spinal cord, Torg's ratio and space available for cord (SAC) at C3-C5 cervical spinal levels.*

	MSD of vertebral body		MSD of spinal canal		MSD of spinal cord		Torg's ratio		SAC	
	M	F	M	F	M	F	M	F	M	F
C3	1.55	1.39	1.20	1.21	0.73	0.70	0.79	0.88	0.47	0.51
C4	1.53	1.37	1.13	1.16	0.78	0.69	0.75	0.86	0.35	0.47
C5	1.52	1.37	1.12	1.12	0.69	0.68	0.74	0.83	0.43	0.44
C6	1.57	1.40	1.13	1.11	0.65	0.64	1.09	1.23	0.49	0.46
C7	1.54	1.38	1.22	1.19	0.60	0.58	0.80	0.87	0.62	0.61
Mean ± SD	1.54±0.18	1.38± 0.15	1.16±0.18	1.16 ±0.15	0.69±0.21	0.66±0.08	0.84±0.19	0.94±0.19	0.47±0.29	0.50±0.15

spinal canal stenosis. The importance of Torg's ratio in spinal canal stenosis has considerably been evaluated by many researchers since then.[13,14,15] These studies have found that Torg's ratio is better than sagittal spinal canal diameter in diagnosing the severity of stenosis of spinal canal in cervical region. Although Torg et al and Parlov et al have found that the normal value of Torg's ratio is 1 in American population and is independent of gender variations. However many recent studies have shown that Torg's ratio differs not only in individuals of different ethnicity but also shows gender variations in the same population. It is seen that Torg's ratio is smaller in men than in women.[16,17] Similar results are found in present study showing that females had a higher Torg's ratio than men due smaller size of vertebral body in females than in males. (Figure 3)

The space available for cord (SAC) is another important parameter to determine the risk of neurological injury. It provides information regarding the functional reserve that is available for movement of spinal cord and changes occurring due to trauma, aging and inflammatory conditions.[21,22] Unlike Torg's ratio which depends more on sagittal vertebral body diameter, the SAC depends more on sagittal spinal canal diameter and shows less variability than Torg's ratio. Research has shown that a low value of SAC has increased risk of neurological injury of cervical spinal cord and its recurrence.[22] Individuals with less SAC are more at risk of developing spinal canal stenosis with lesser degree of pathological changes like facet joint arthrosis, osteophytes, disc herniation etc. Herzog RJ et al suggested that SAC is especially significant if Torg's ratio is <0.8 or the sagittal cervical spinal canal diameter is < 12.5mm in symptomatic individuals.[11]

Conclusion

It is concluded that MRI is more reliable imaging modality for morphometric analysis of cervical spine than plain radiography. The sagittal vertebral body diameter show gender variations and is more in males than in females resulting in high value of Torg's ratio in females. Thus Torg's ratio cannot be used as a reliable parameter for assessment of spinal canal stenosis as it may over diagnose cervical canal stenosis in males. On the other hand, sagittal diameter of spinal cord and spinal canal did not show any gender dimorphism, resulting in less variability in SAC values. It is also found that the value of Torg's ratio and SAC is smaller in our study as compared to other studies of this region.

Abbreviations

SAC: Space available for cord

MSD: Mid sagittal diameter

MRI: Magnetic resonance imaging

FSE: fast spin-echo sequence

TR: repetition time

TE: echo time

FOV: field of view

FRFSE: fast recovery fast spin-echo

Conflict of Interest: None

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Authors Contribution

M K, R R: Conceptualization of Project,
M K, R R, K R: Data Collection
R R, K R: Literature Search
K R, S M R, H M: Statistical Analysis
S M R, H M: Drafting, Revision
M K, R R, S M R, H M. Writing of Manuscript

Esculapio - Journal of Services Institute of Medical Sciences

Original Article

A Profile of Neonatal Admissions and Mortality in Tertiary Care Hospital of Faisalabad

Sulman Javaid,[1] Muhammad Tauseef Omer,[2] Muhammad Ahsan ul Haq[3]

Abstract

Objective: To study the profile of neonatal admissions and their outcome in a tertiary care hospital.

Methods: The study was conducted in the Neonatal Unit of The Children's Hospital, Faisalabad for one year from 1st Jan 2020 to 31st Dec 2020. Data of all admitted patients during the study period were reviewed and analyzed in terms of demographics, weight, diagnosis, and outcome. The diagnosis was made on clinical features, laboratory reports, and radiological findings. SPSS version 25 was used for data analysis.

Results: Out of 2662 neonates admitted during the study period, 35 were excluded. Out of the 2613 neonates, there were 1824 (69.8%) males and 789 (30.19%) females. There were 2355 (90.12%) full-term while 258(9.87%)babies were preterm neonates. Low birth weight (LBW) babies were 1216 (46.53%) of total cases. The newborns presenting within the first 24 hours of life were 319 (12.2%). Birth asphyxia was the commonest diagnosis at admission accounting for 807 cases (30.88%), followed by neonatal sepsis 751(28.74%) and prematurity 258(9.87%). Out of 2613 babies,1682 (64.4%) were discharged, 232(8.9%) left against medical advice, and 699 (26.8%) neonates expired. Among cases who died, the highest contribution was observed from birth asphyxia in 294 cases (42.60%) followed by neonatal sepsis 211 cases (30.18%) and prematurity 133 cases (19.02%).

Conclusion: Birth asphyxia, prematurity, and sepsis constitute three-fourths of hospital admissions in our neonatal unit. The most common cause of mortality was birth asphyxia followed by prematurity and neonatal sepsis.

Keywords: Birth asphyxia, Prematurity, Sepsis, Tertiary care hospital

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Introduction

Neonatal age is defined as the initial 28 days of life.[1] Neonatal mortality is defined as the death of a newborn within the initial 28 days of life.[2] This initial phase of life is very crucial for survival due to the susceptibility of neonates to a variety of illnesses.[3]

According to UNICEF, globally about 5.6 million children died before reaching 5 years of age out of which 2.6 million deaths occurred within the first month of life.[1,4] When we look at local data, WHO estimates the under 5 mortality rate in Pakistan to be 81/1000 live births with neonatal deaths (46/1000 live births) being the major contributor.[5]

This figure is almost 4 times the target of sustainable development goals (SDG) that eyes a reduction of mortality rate due to preventable deaths to at least 12/ 1000 live births by 2030.[6]

Although simple measures like improvement of the hygienic condition, neonatal resuscitation at birth, improvement of antenatal care.[7] improvement of antenatal care, exclusive breastfeeding till 6 months of age can significantly reduce the neonatal mortality.[1,8]

However, the lack of access to health, poor education, and financial constraints are major hindrances to achieve the targets in Pakistan.[9]

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To achieve the reduction of neonatal mortality, we have to improve the neonatal services by capacity building of health care workers through imparting knowledge, resources, expertise, and tools.[10]

The reduction of neonatal mortality is not possible without the awareness of the causes of neonatal admissions and mortality in our settings. Hence, to identify the major reasons for neonatal admission and mortality, this study was conducted in a tertiary care referral hospital.

Methods

This descriptive observational study was conducted in the Neonatal Unit of The Children Hospital, Faisalabad. The hospital is a tertiary care hospital that receives only the out-born neonates. We reviewed the data from 1st January 2020 to 31st December 2020. The study was initiated after seeking permission from the Institutional Review Board. All the admitted neonates in the neonatal unit were included in the study. Data of all admitted neonates from 1st January 2020 to 31st December 2020 were included in the study. The data was collected from the admission register of the unit and entered on Performa. Neonates with incomplete data were excluded subsequently.

Following operational Definitions were applied:

Neonate: was defined as a baby up to the first 28 days of life.

Low birth weight (LBW) birth: weight less than between 1501 to 2500g

Very low birth weight (VLBW) weight: birth weight between 1.01 to 1500 grams

Extremely low birth weight (ELBW) weight: birth weight of less than 1000grams.

Preterm/Premature: neonate born before 37 completed weeks

Asphyxia Neonatorum (ANN): History of delayed cry at birth.

Sepsis: History and examination supported by complete blood count with platelets, C reactive proteins (CRP), and positive blood, urine, or cerebrospinal fluid (CSF) culture.

Congenital heart disease (CHD): confirmed with echocardiography.

Acute watery diarrhea (AWD): was described as loose watery stools.

Meconium aspiration syndrome (MAS): was diagnosed on the history of being born through meconium-stained amniotic fluid, respiratory distress, and chest radiograph.

Bronchopneumonia: clinical and radiological findings of consolidation.

Neonatal jaundice: Serum bilirubin in the pathological zone in age, weight, and gestation specific range.

Congenital malformations: neonates with different anomalies and syndromic features.

Meningitis: was diagnosed on basis of clinical findings and CSF complete examination.

Respiratory distress syndrome: was diagnosed on basis of history, clinical examination, and chest X-ray.

The other conditions like Infant of a diabetic mother, metabolic disorders, urinary tract infections, Bleeding disorders, tetanus, acute renal failure, and seizure disorder were included in others and diagnosed clinically and confirmed with relevant laboratory investigations.

Data Analysis

Both quantitative data (age, gestational age, and weight) and qualitative data (gender, final diagnosis, and outcome i.e. neonates who were discharged, left against medical advice, or died) were recorded on a Performa. All data were entered and analyzed using computer software SPSS version 25.

Results

A total of 2662 neonates were admitted to our unit from 1st January 2020 to 31st December 2020. A total of 35 cases were excluded due to incomplete data and 2613 cases were included for the study.

Out of 2613 neonates, there were 1824 (69.8 0%) males and 789 (30.19%) females the male: female ratio was 2.3: 1.

There were 2355 (90.12%) full-term and 258 (9.87%) preterm neonates. A total of 1303 (49.86%) babies presented to our unit between 8 to 28 days of life, while 319 (12.20 %) babies presented in the first 24 hours of life.

The commonest diagnosis was birth asphyxia 807 cases (30.88%), Neonatal Sepsis was diagnosed in 751 cases (28.74%), and 258 cases (9.87%) presented with prematurity. hyperbilirubinemia, Acute Watery Diarrhea, and Bronchopneumonia were seen in 407 (15.57%), 161 (6.16%), and 65 (2.48%) cases respectively. A

total of 1216 cases (46.5%) were in low birth weight category.

The outcome data revealed that 1682 cases (64.4%) were discharged, 699 cases (26.8%) expired, 232 cases (8.9%) left against medical advice; the highest proportion of mortality was frombirth asphyxia 294 cases (42.60%), followed by Sepsis 211 cases (30.18%) and prematurity 133 cases (19.02%).

Discussion

Our study was performed to determine the profile of admission and outcomes in a tertiary care neonatal unit. We determined that about twice as many males got admitted in the unit as compared to females which is consistent with regional studies revealing gender preference favoring male babies.[11] However, the ratio of females was greater than males in a study performed in Islamabad that may be attributed to the small sample size.[12]

Out of the total pool, the number of low birth weight babies (< than 2.5 kg) was 1216 (46.53 %). Klemm found a similar percentage of 55.3% in Bangladesh.[13] In an Indian study, a higher percentage (60.62%) of low birth weight babies was noted.[14]

Table 1: *Demographic Data*

		Frequency (n)	Percentage (%)
Age (Days)	< 1 day	319	12.2%
	1-3 days	380	14.5%
	4-7 days	581	22.2%
	8-28 days	1303	49.9%
	> 28 days	30	1.1%
Gender	Male	1824	69.8%
	Female	789	30.2%
Gestational Age (Weeks)	<28 wks	16	0.6%
	28-32 wks	75	2.9%
	32-37 wks	356	13.6%
	37-42 wks	2164	82.8%
	> 42 wks	2	1%
Weight (kg)	< 1 kg	21	0.8%
	1-1.5 kg	153	5.9%
	1.5-2.5 kg	1042	39.5%
	2.5-4 kg	1373	52.5%
	> 4 kg	24	0.9%

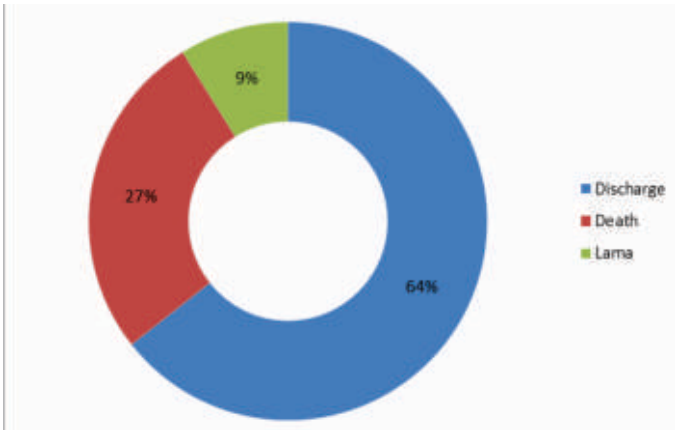

Figure 1: *Clinical Outcome*

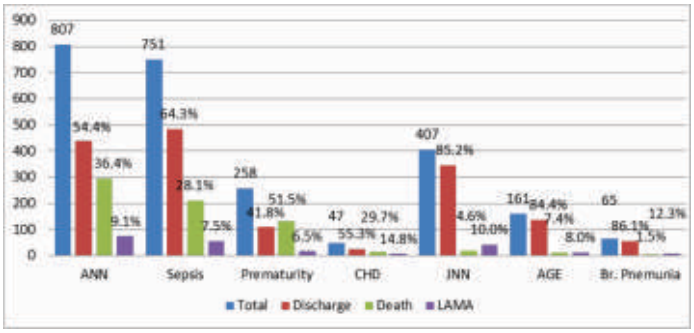

Figure 2: *Graphical Representation of Neonatal Admission & Outcome*

This difference can be explained as almost 48 percent of the study population in the Indian study was preterm as compared to 9.47% preterm babies in our study. Low birth weight babies are prone to morbidity and mortality that explains the high burden of these babies seeking admission in neonatal units.[15]

As we look at the age of admission, the highest number of newborns (49.86%) presented between 8 to 28 days of life, while 12.20% of babies presented within the first 24 hours of life. This pattern is consistent with the results of regional referral hospital studies that receive only out-born neonates like our unit.[1] On the contrary, Begum et all found 81.3 % of neonates got admitted in the neonatal unit within the first 24 hours of age. This difference can be explained as these study centers receive both inborn and outborn neonates.[16]

The leading cause of admission in our study was birth asphyxia that constituted 30.88% of patients. Our finding conforms with local studies like Lahore 31.89%, Multan 34.5%.[1,17] The high index of birth asphyxia may be attributed to the fact that about half of the deliveries are conducted outside health facilities, thus lack of proper health care at the time of birth is the major cause of the high burden of asphyxiated babies.[1]

Neonatal sepsis was observed in 28.74% in our study which is in conformity with studies conducted by Ali SR in Karachi with 20.3% and a study held in South Africa with 21%.[18,19]

The percentage of septic neonates was 33.8% in Abottabad and 38% in an Indian study. This difference may be explained as neonatal meningitis, cellulitis and bronchopneumonia were also counted under sepsis rather than separate entity ad in our study.[20,21]

Prematurity contributed to 9.87% of our admissions. This finding is similar to the 13% noted by Narayan in India.[26] However, as we look at local data, the frequency of admissions with prematurity were 21.47%, 20%, and 27.9% were observed by Khan, Quddusi, and Ali SR respectively. The difference may be since our study center receives only the outborn / referred cases.[18,20]

The outcome data shows that 64.4% patients were discharged and 26.8% patients expired which is similar to findings of Karachi and Larkana with observed mortality rate of 25.85% and 38 % respectively.[23,24]

Birth Asphyxia, Sepsis, and prematurity were leading causes of mortality, responsible for 39.9%, 30%, and 17.9% of deaths. This is similar to studies conducted in developing countries.[1,24]

A total of 8.9% cases left against medical advice, which is much lower than reported elsewhere (from 20.25% to 26.2%). The main reason of leaving against medical advice was poor socioeconomic status and perceived poor outcome of the patient.[1,17,25]

Conclusion

Birth asphyxia, prematurity, and sepsis constitute three-fourths of hospital admissions in our neonatal unit. The most common cause of mortality was birth asphyxia followed byprematurity and neonatal sepsis.

Conflict of Interest: None

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Authors Contribution

S J: Conceptualization of Project,

S J, M T O, M A U H: Data Collection, Literature Search, Statistical Analysis, Drafting, Revision, Writing of Manuscript

Esculapio - Journal of Services Institute of Medical Sciences

Original Article

Bacterial Infections in Covid-19 Patients Admitted in Intensive Care Units of a Tertiary Care Hospital

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Abstract

Objective: To detect presence of bacterial infections in RT-PCR confirmed Covid-19 patients.

Methods: This is a retrospective study of the data from 246 RT-PCR confirmed Covid-19 patients, admitted to ICUs of Mayo Hospital, Lahore from 1st April 2020 to 30th September 2020 and conducted in the department of Pathology, King Edward Medical University, Lahore. Bacterial infections were determined by characteristic clinical features and positive bacterial cultures. The data was extracted from the record of ICUs of Mayo hospital and Microbiology laboratory record with a standardized data collection form. The ethical approval was obtained from institutional review board of King Edward Medical University, Lahore.

Results: Bacterial infections were detected in 32.5% patients. Tracheal secretions were the most frequent source, representing 51.3% of all the infections, followed by pus 16.2%, urine 13.5%, blood 12.1%, pleural fluid 4%, sputum and cerebrospinal fluid (CSF) constituting 1.3% Klebsiella pneumoniae was the most frequently isolated organism (28.4%), followed by Pseudomonas 24.4%, Eschericia coli 22.9%, Staphylococcus aureus 8.1% and Acinetobacter baumanii 8.1%, Citrobacter freundii 6.8%, Salmonella typhi 1.3%. Bacterial infections were frequent in age group 60-70 years.

Conclusion: Bacterial infections in patients of Covid-19 are not uncommon. These can lead to increased morbidity and mortality.

Keywords: Bacterial infections, COVID-19, Severe acute respiratory syndrome (SARS), Intensive care units (ICUs).

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Introduction

Severe acute respiratory syndrome corona virus-2 (Covid-19) is a newly emerged viral infection. Viral-bacterial co-infections are one of the key medical concerns, leading to increased morbidity and mortality rates.[1] Secondary and co-bacterial infections particularly with Streptococcus pneumonia were responsible for most of the fatalities during the influenza outbreak of 1918. The increased mortality in the 2009 H1N1 Influenza pandemic was also associated with bacterial co-infections. 20-30% of patients presenting with influenza have superimposed bacterial infections.[2] Similarly, children suffering from respiratory syncytial virus infections are more prone to superimposed bacterial pneumonia in more than 30% of the cases.[3] The importance of bacterial co-infections in the severity of respiratory diseases is well established but despite that their association and outcomes are not well studied during large outbreaks of respiratory viral infections.[4]

Langford et al. differentiated bacterial co existing infections from secondary infections. Variable results

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were reported in a meta-analysis of 3448 hospitalized patients from 28 studies in Asia. Eight (8) studies described secondary bacterial infections developed during hospitalization while 20 studies showed bacterial co-infections.[5] Klebsiella pneumoniae. Eschericia.coli, Pseudomonas, Acinetobacter, Hemophilus influenzae, Serratia, Enterobacter cloacae, Methicillin resistant Staphylococcus aureus (MRSA), Methicillin sensitive Staphylococcal aureus (MSSA) were the isolated organism according to a study.[6]

There are certain important limitations of the studies investigating bacterial infections in Covid-19 patients. Existing data available on bacterial infections in Covid-19 patients is scanty both geographically and temporally all over the world. This fact highlights the importance of more data analysis on coexisting bacterial infections to highlight their significance in Covid-19 mortality and morbidity.[7]

As no comprehensive data is available on the subject in our set up too and this knowledge gap has important implications, so the present study was conducted to get an estimate of bacterial infections in patients admitted in ICUs of Mayo hospital, Lahore.

Methods

A retrospective analysis of all the PCR confirmed patients of Covid-19, admitted in ICUs of Mayo Hospital, Lahore from 01.04.2020 - 30.09.2020 conducted at Department of Pathology, King Edward Medical University/Mayo hospital Lahore. Patients of all ages and both genders with symptoms of respiratory and non-respiratory bacterial infections were included. Suspected cases of Covid-19 and patients admitted in ICUs for non-Covid-19 conditions were excluded.

Data was obtained and extracted by one reviewer and was cross checked by another reviewer. The patient's identification done by using the admission record of all patients with Covid-19 infection, admitted to Mayo hospital ICUs. Demographic factors including age, gender, and clinical factors, including comorbid conditions like hypertension, diabetes, asthma, chronic obstructive pulmonary disease was noted from medical records of ICUs.

Laboratory data was extracted from Microbiology laboratory record with a data collection form especially designed proforma for this purpose. The ethical approval was obtained from institutional review board of King Edward Medical University, Lahore.

Statistical analysis

Categorical variables like gender, comorbid conditions, sample type and bacterial growth were expressed as percentages. Continuous variables like age, were analyzed and expressed as mean. Categorical variables like gender, comorbid conditions (like diabetes, hypertension, and asthma), sample type (source of sample) and bacterial growth were compared by using chi-square ($\chi 2$) test. The 95% confidence interval with a p-value of < 0.05 was considered statistically significant. The SPSS software version 23.0 for windows was used for statistical analysis.

Results

Total 339 patients tested positive via RT PCR for Covid-19 were evaluated. We included total 246 patients after excluding the 93 patients with incomplete record. The patient age ranged from 32 -74 years. The mean age ± SD was 5.83 ± 11.84. Male to female ratio was 2:1. The comorbid conditions recorded were diabetes, hypertension, chronic obstructive disease, and asthma. One hundred twenty three covid-19 patients (50%) had Diabetes mellitus and hypertension was found in 175 Covid-19 patients (70%). Chronic obstructive disease and asthma were seen in 15 of the 246 Covid-19 patients (21%). The concomitant bacterial infection was seen in 74 Covid-19 patients (32.5%).

Respiratory secretions were the most frequent source, representing 52.3% of all the co-infections, followed by pus 16.8%, urine 13.5%, blood 12.1%, pleural fluid 4% and last of all sputum and CSF constituting 1.3%. The most frequent organism isolated was Klebsiella pneumoniae 28.3%, followed by Pseudomonas aeruginosa 24.3%, Escherichia coli, 22.9, Staphylococcus aureus 8.5% and Acinetobacter baumanii 8.0%, Citrobacter freundii 6.7%, Salmonella typhi 1.3%. In present study bacterial coinfections were found to be more prevalent in age group 60-70 years.

Discussion

This single center study analyzing the data retrospectively determined that coexisting bacterial infections in patients with Covid-19 is not uncommon especially in patients admitted in ICUs. Currently, there is inadequate data about bacterial co-infections in Covid-19 across the world.

In our study the rate of bacterial co-infection was found in 74 patients out of 246(32%). The results of study conducted in Washington revealed that bacterial co-

infection was present in 4.8% of the patients.[8] This is relatively lower to the coinfection rate calculated in our study (32.5%). Most of the studies from China and Spain shown equally lower coinfection rates.[9,10,11,12] In another metanalysis, only 7% admitted patients in intensive care units and non-intensive care units' Covid-19 patients showed bacterial concurrent infection.[13] The most suitable explanation for this difference in bacterial co-infections is a comparatively sicker patient population with hypertension and diabetes mellitus. Half of the (50%) patients had diabetes and 70% showed hypertension while 21% were having chronic obstructive disease and asthma in our study. Patients with cardiorespiratory and metabolic comorbidities are predisposed to bacterial co-infections while suffering from viral infections, due to a dysfunctional and dysregulated immune response. It is a well-known fact that Diabetes mellitus itself down regulate effective T cell and neutrophil reaction.[14] As a result, ineffective chemo taxis, decreased bactericidal activity of neutrophils/ macrophages and defective phagocytosis leads to diminished innate immune response, causing susceptibility to secondary bacterial infection.[15]

Respiratory bacterial co-infections were the most frequently observed infections in COVID-19 patients admitted in ICUs in our study. Our study identified Klebsiella pneumoniae as the most frequent respiratory pathogen, followed by Pseudomonas, Escherichia coli, Staphylococcus aureus, Citrobacter and Acinetobacter as the less commonly isolated respiratory pathogens.

While other studies reported Haemophilus influenzae, Mycoplasma pneumoniae and Pseudomonas aeruginosa.[16] Skin Infections were the 2nd common bacterial infections in Covid-19 ICU admitted patients constituting 16.2% with bacterial profile of Pseudomonas aeruginosa, Klebsiella pneumoniea, Eschericia coli, Acinetobacter, Staphylococcus Aureus. UTIs constituted 13.5% of all the infections with Eschericia coli as the most common organism. Rest of the spectrum comprised of Klebsiella pneumoniae and Pseudomonas aeruginosa.

The organisms isolated in UTIs can be due to a variety of conditions varying from asymptomatic bacteriuria, lower urinary tract infections to acute pyelonephritis. It has been studied that predisposition to such infections can point toward a malfunctioning primary mucosal immune system with subsequent inability to discriminate and build a response to commensal bacteria.[17] Relatively higher incidence of diabetes mellitus in our study may be another probable justification for increased rates of urinary tract infections in the studied population. Furthermore, it was observed in our study that patients who had bacterial infections were relatively older. The elderly population is known to have amplified proinflammatory cytokines and reduced anti-inflammatory cytokines. Other age-related pathophysiological processes providing explanation to our results are modification of angiotensin converting enzyme-2(ACE-2) receptors' expression, altered autophagy and increased production of reactive oxygen species.[18]

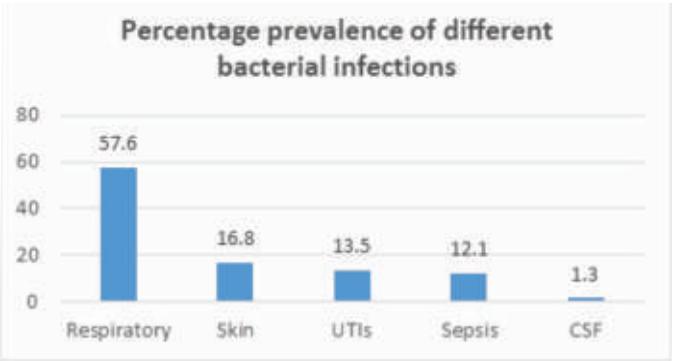

Figure.1 *Percentage Prevalence of different Bacterial Infections in Covid-19 Patients.*

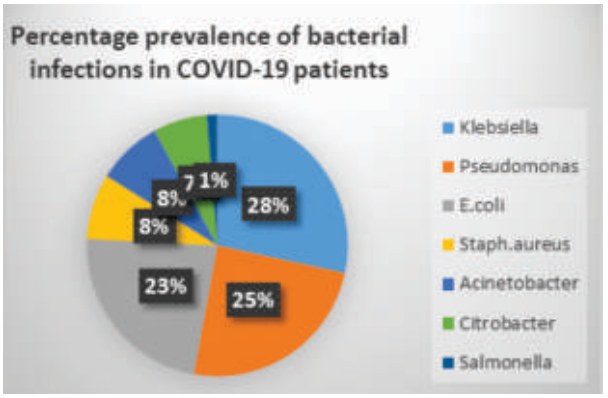

Figure.2 *Percentage Prevalence of Bacterial Infections in Covid-19 Patients*

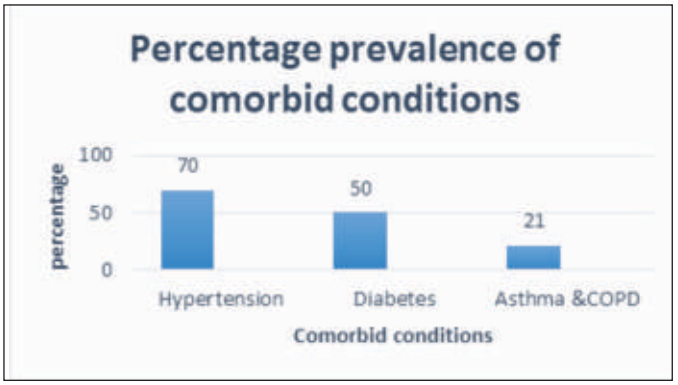

Figure.3 *Percentage Prevalence of Comorbid Conditions*

Limitation of the study

Though this study was conducted in a big tertiary care hospital, but it was a single center study limiting the sample size. The studied population was predominantly from Lahore and only patients admitted in ICUs were included in study, thus limiting the generalizability of the data.

Conclusion

Concomitant bacterial infections in patients with COVID-19 are not uncommon among the Covid-19 patients admitted in intensive care units.

Strengths of the study and recommendations

As the study determined that concomitant bacterial infections are common especially among Covid-19 patients admitted in ICUs, this finding highlighted the importance of the culture surveillance of such bacterial infections. Therefore, it is recommended that suspected cases must be confirmed through bacterial culture surveillance so that patients can be managed timely and appropriately for bacterial infections.

More prospective multicenter studies with large sample size, including all the admitted Covid-19 patients in hospital can be conducted to get further clarity on the topic.

Conflict of Interests None

Funding Source None

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Authors Contribution

Q U I: Conceptualization of Project,
Q U I, R S, S A: Data Collection, Review
Q U I, S A: Literature Search
Q U I, S A, R D: Statistical Analysis, Review
Q U I.: Writing of Manuscript

Esculapio - Journal of Services Institute of Medical Sciences

Original Article

Assessment of Impact of Psoriasis on Quality of Life of Patients Using Dermatology Life Quality Index

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Abstract

Objective: To assess the impact of psoriasis on quality of life of patients using Dermatology Life Quality Index (DLQI) score.

Methods: This was a cross-sectional study conducted in the Department of Dermatology, Faisalabad Medical University over a period of six months. 194 patients of psoriasis were enrolled. The disease extent and severity were assessed by physical examination and DLQI questionnaires in Urdu were filled in by the patients. Total scores were calculated and effect on quality of life was noted as No effect at all (0-1), Small effect (2-5), Moderate effect (6-10), Very large effect (11-20) and Extremely large effect (21-30) on patient's life.

Results: Mean age of the patients was 31.8±11.0 years. Mean DLQI score was 10.7±5.9. Out of 194 patients, 104 (53.6%) were males while 90 patients (46.4%) were females. Effect of disease on quality of life was noted as: No effect on 25 patients (12.9%), Small effect on 39 patients (20.1%), Moderate effect on 70 patients (36%), Very large effect on 44 patients (22.7%) and Extremely large effect on quality of life of 16 patients (8.3%).

Conclusion: Psoriasis can significantly impair a patient's quality of life. It can have a marked psychological impact as most of the patients reported moderate to severe impairment of quality of life.

Key words: Psoriasis, Quality of life, Dermatology Life Quality Index (DLQI)

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Introduction

Psoriasis is a psycho-cutaneous disorder triggered by psychological factors.[1] It is a common disorder with a prevalence of around 2%. It is characterized by scaly, erythematous plaques involving limited to large areas of body.[2] The chronic nature of the disease, the lack of a universally effective treatment and the unpredictable course of the disease is frustrating for patients with psoriasis. Patients suffer from poor body image and low self-esteem and also experience a considerable level of psychological burden.[3]

Recently, the importance of Psychodermatology has been highlighted.[4] Therefore, psoriasis could be considered as a psychosomatic disorder, which means physical and psychological factors concomitantly are involved in appearance, progression, relapse and remission of psoriasis.[1] Quality of life is a multidimensional index of social, behavioural and cultural factors and is currently a scientifically measurable tool that can be validated. The Dermatology Life Quality Index (DLQI) is used to measure it, which was proposed by Finlay et al. in 1994.[5] This 10-item questionnaire was applied in many studies, its validity and reliability in cutaneous disorders is proven.[6,7]

The psychological issues reported in psoriasis include depression associated with social stigmatization.[8] Dalgard et al, conducted a multicentre study across 13 European countries and reported various psychological

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morbidities associated with psoriasis including depression, anxiety, suicidal tendency, addiction and sexual dysfunction.[9]

The purpose of this study was to assess the quality of life in psoriasis patients in our population and to assess the psychological impact on patient`s personal and social life. By knowing the magnitude of the problem, Dermatologists can play an important role in reducing the anxiety and misery of patients and help them better cope with their appearance and psychosocial issues. This may eventually lead to better management of this psychosomatic disorder.

Methods

After getting approval from Ethical Review Board, patients were selected by non-probability consecutive sampling from the Outpatient Department of Dermatology, Faisalabad Medical University from May 2020 to November 2020. Inclusion criteria included adult patients from 16 to 60 years of age, who were diagnosed cases of Psoriasis on basis of presence of erythematous, scaly plaques on body and having the disease more than one year. Patients who were excluded from the study were; psychiatric patients who couldn't answer the questionnaire properly, patients taking psychoactive drugs and patients having any other co-existing chronic disease such as diabetes mellitus, hypertension, peri-pheral vascular disease etc which may contribute to altered quality of life.

After taking written informed consent, 194 patients of psoriasis were enrolled. Their demographic data was registered on predesigned proformas. The severity and extent of disease was noted by physical examination. Patients were asked to fill the DLQI questionnaire Urdu version, after explaining the purpose of research and method of filling the questionnaire. After collecting the questionnaires from patients scoring was done for each question and total score and effect on quality of life of patients was noted.

DLQI questionnaire is divided into 10 questions, involving six domains, including symptoms and feeling, daily activities, leisure, work and school, personal relationships and treatment difficulties, each question with 4 possible answers scored from 0 to 3. The DLQI score is calculated by summing the scores of all the questions, resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. DLQI score is stratified into the five following levels: 0-1= no effect, 2-5 = small effect, 6-10= moderate effect, 11-20 = very large effect, and 21-30 = extremely large effect.[10]

Data was entered and analysed using SPSS Vs 27. Descriptive statistics was calculated for all variables. Mean and standard deviation was calculated for all quantitative variables like age and score of questionnaires. Frequency and percentages were calculated for qualitative variables like gender and effect (No, Mild, Moderate, Very large or Extremely large effect) on quality of life of patients.

Results

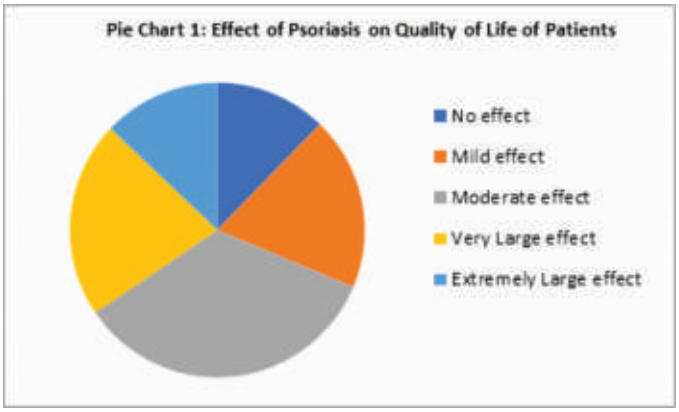
A total of 194 patients were included in the study during the study period of six months. Mean age of the patients was 31.8±11.0 years. Out of 194 patients, 104 (53.6%) were males while remaining 90 patients (46.4%) were females. 128 patients (66%) had the illness for 1-3 years while 66 patients (34%) had the illness for 4-8 years. 98 (50.5%) patients were married, 77 (39.7%) were unmarried, 13 (6.7%) were divorced and 6 (3.1%) were widows. Analysis of occupational status revealed that 62 patients (32%) were employed and 132 patients (68%) were unemployed. Majority of the patients 130 (67%) were illiterate while 33% were educated. Majority of the patients (60.8%) were 16-30 years old age and rest (39.2%) were 51-60 years old (Table-1).

Table 1: *Descriptive Demographic Data of Patients*

		No. of Patients (n = 194)	
		n	%
Gender	Female	90	46.4
	Male	104	53.6
Age	16–30	18	14.4
	31-60	06	4.8
Marital status	Married	98	50.5
	Divorced	13	6.7
	Widow	6	3.1
	Unmarried	77	39.7
Duration of disease	1-3 years	128	66
	4-8 years	66	34
Effect of disease	No effect	25	12.9
	Mild effect	39	20.1
	Moderate effect	70	36
	Very Large effect	44	22.7
	Extremely Large effect	16	8.3

Mean DLQI score was 10.7±5.9. Effect of disease on

quality of life was as follows: 25 patients (12.9%), Small effect on 39 patients (20.1%), Moderate effect



on 70 patients (36%), Very large effect on 44 patients (22.7%) and Extremely large effect on quality of life of 16 patients (8.3%) as seen in Pie chart 1.

Discussion

In our study, effect of disease on quality of life was noted as: No effect on 25 patients (12.9%), Small effect on 39 patients (20.1%), Moderate effect on 70 patients (36%), Very large effect on 44 patients (22.7%) and Extremely large effect on quality of life of 16 patients (8.3%). That means 60 (31%) patients had a DLQI score >10 which indicates very large to extremely large impact of the disease on quality of life. These findings are very close to the results of Barot et al[11] where they reported DLQI score >11 in 31.7% of the patients.

We found that mean DLQI score in our study population was 10.7±5.9. This was higher than that reported by Mazotti et al[12] who studied effect of psoriasis on quality of life of 900 patients. This difference was probably because of larger sample size and different ethnic background of the study populations. Our results were comparable to those of Khan et al[13] and Eghileb et al[14]. However, our mean DLQI was lower than those reported by other researchers[15-18] across the world, who reported poorer quality of life in patients of psoriasis in their respective populations. These variations can be attributed to different sociocultural norms and demographic variations of the respective populations. Psoriasis is a common skin disease with an unknown aetiology and unpredictable course which leads to a particularly huge dilemma especially in darker races like ours where beauty and complexion have conven-tional standards and enormous psychosocial impact.

In our part of the world, psoriasis is considered as an infectious skin disease by many people. This results in social isolation of the patients. These factors can seriously impair the social life of psoriasis patients especially the females. Since stress has a profound effect on causation and aggravation of diseases like psoriasis and this can lead to difficulty in management of patients. Therefore, while treating these patients their psychological wellbeing must be considered. Involvement of a psychologist and even a psychiatrist in special cases is inevitable. Psoriasis support group should be available and all psoriasis patients should be encouraged to join these groups.

Conclusion

Psoriasis has a significant impact on psychosocial life of patients as most patients reported moderate to extremely high negative impact on their lives. Dermatologists should pay more attention towards this aspect of the disease and treat it appropriately with available modalities.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

A K: Conceptualization of Project,
A M: Data Collection
A H: Literature Search
A S: Statistical Analysis
M S: Drafting, Revision
H T: Writing of Manuscript

Esculapio - Journal of Services Institute of Medical Sciences

Original Article

Frequency of Iron Deficiency Anemia in Children Presenting with Febrile Seizures

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Abstract

Objective: The objective of the study was to find out the frequency of iron deficiency anemia in children presenting with febrile seizures in Services Hospital, Lahore

Methods: This observational study was conducted in department of Pediatrics Services Hospital Lahore from May 2018 to November 2018. A total of 310 children fulfilling the inclusion and exclusion criteria admitted in Pediatric Unit-1 of Services Hospital, Lahore were enrolled. Informed consent from parents of children was taken to include their data in the study. Demographic profile age, gender, was recorded. From every patient, 5 cc blood was drawn and sent to the laboratory to determine the serum iron level. Data was recorded on predesigned proforma. The collected data was analyzed through SPSS version 16.

Results: In our study, out of 310 cases, 34.84 %(n=108) were between 6-30 months of age while 65.16%(n=202) were between 31-60 months of age, mean +SD was calculated as 36.14+12.99 month, 42.90%(n=133) were male and 57.1%(n=177) were females. Frequency of iron deficiency anaemia in children presenting with febrile seizures in services hospital, Lahore was found out to be 14.84 %(n=46).

Conclusion: Frequency of iron deficiency anaemia is 15% in children with febrile seizures

Keywords: Febrile seizures, iron deficiency anaemia, Pakistani Children

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Introduction

Febrile seizure (FS) is the commonest type of fits in children, occurring in 2-5% of children from 6 months to 6 years of age who are otherwise neurologic ally normal.[1] Febrile seizures are defined as seizures taking place in children classically 6 months to 5 years of age having temperature more than 38°C[2], and not having any evidence of brain pathology (e.g. meningoencephalitis, head injury, and epilepsy) or any known cause of seizure (e.g. electrolyte imbalance, hypoglycemia, drug use, or drug withdrawal), or a previous history of a seizure without fever.[3,4] Febrile seizures are prevalent worldwide but frequency is more in Asian children.[5]

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Iron deficiency is a very common micronutrient deficiency affecting more than one-third of the world population and involves all age groups. Most children with iron deficiency may present with anaemia but iron deficiency also involves other organs and systems of the body as well. Iron deficiency in children is associated with decreased attention span and poor school performance. Iron deficiency may affect the developing brain and may result in altered development of many brain tissue like hippocampus neurons, brain myelination etc. It also results in disturbances in energy metabolism, weak visual and auditory evoked potentials and alterations in synaptic neurotransmitter systems including Norepinephrine, Dopamine, Glutamate, Gamma-Amino Butyric Acid (GABA) and serotonin.[6,7] the bad effects of iron deficiency on central nervous system are further aggravated by high temperature.[8]

A lot of work has been done to find out association between febrile fits and iron deficiency and results are conflicting.[1,9,10] In most researches done in the past, iron levels were compared in those who were having and not having febrile fits. A recent study[1] revealed that iron deficiency anaemia was 22% in children with febrile seizure, while two other studies recorded 31.2%[6] and 15%.[11] A local study conducted in Faisalabad[11]

showed that only 5.3% of the patients with febrile seizures are iron deficient while another study done in Rawalpindi showed a statistically significant relationship between febrile fits and low serum ferritin (P-Value 0.028).[12]

The rationale of the present study is that there is a need to conduct further studies on this topic as previous studies have shown considerable variation in results (ranging from 31.2% to 5.3%) so that the relationship of febrile seizures and iron deficiency anemia can be better evaluated. This study can provide evidence-based information so that further strategies in management of febrile seizures can be established. The study from Faisalabad has shown a very low incidence which demands further exploration as iron deficiency is presumed to be higher in developing countries.

Methods

This cross-sectional study was conducted in Department of Pediatrics, Services, Hospital, Lahore from May 2018 to November 2018 Ethical approval was taken from the institutional review board.

Diagnosed cases of febrile seizures of both genders from 6 months to 60 months were included in the study. However, all diagnosed cases of previous febrile seizures, those on treatment of iron deficiency anemia (on history and medical record), those with CNS malformation (on previous medical records) or CNS infection by CSF examination (on lumbar puncture), having history of premature birth (<37 wks) or low birth weight (2.5kg), and malnourished and developmentally delayed children were excluded from study.

By using the Non-probability consecutive sampling technique, a total of 310 cases meeting the inclusion and exclusion criteria were included. Informed consent of the parents of children was obtained to include their data in the study. Demographic profile age, gender, was recorded. A 5-cc blood in a sterilized syringe was taken from each child with the help of paramedical staff and sent to the hospital laboratory and to an another private lab to determine the iron deficiency anaemia, and on receiving the laboratory reports presence/absence of Iron deficiency anemia was recorded on a pre-designed proforma. Iron deficiency anemia was diagnosed on the basis of hemoglobin and iron levels.

The data was analyzed through SPSS version 16. Mean and standard deviation were calculated for age. Frequency and percentage were calculated for categorical variable i.e. gender and presence/absence of iron deficiency anemia. Data was stratified for age and gender, breast fed/formula fed, economic status (monthly income <10,000 11,000-20,000 >20,000). Chi-square test was used. P-Value < 0.05 considered as significant.

Results

Age distribution of the patients was done, 34.84% (n= 108) were between 6-30 months of age while 65.16% (n=202) were between 31-60 months of age, with a mean+SD age of 36.1+13.0 months. There were 42.9% (n=133) male while 57.1%(n=177) were females.

Frequency of iron deficiency anemia in 310 children presenting with febrile seizures in services hospital, Lahore was recorded in 14.84%(n=46) while 85.16% (n=264) had no findings suggestive of iron deficiency. (Fig 1)

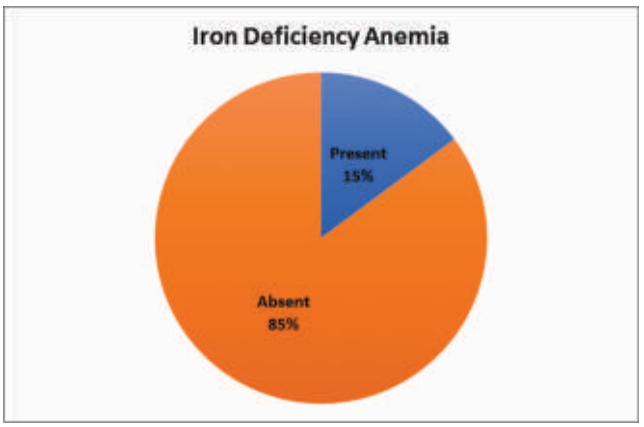

Figure 1: *Frequency of Iron Deficiency Anemia Among Children with Febrile Seizures*

Stratification for iron deficiency anemia in children presenting with febrile seizures with regards to age, gender, milk feed and Income were recorded and presented in Table 1. The gender, age, milk feeding practice group had no difference for frequency of iron deficiency anemia while Income groups had significantly different frequency of IDA with p-value < 0.001. The lower the income higher the prevalence of iron deficiency anemia was recorded.

Table 1: *Relationship of Iron Deficiency Anemia with Various Factors Among Children with Febrile Seizures*

Factors	Categories	Iron deficiency Anemia				P-value
		Yes		No		
		n	%	n	%	
Gender	Male	19	14.3	114	85.7	0.812
	Female	27	15.3	150	84.7	
Age	6 – 30	14	13.0	94	87.0	0.497
	31 – 60	32	15.8	170	84.2	
Milk feed	Breast fed	12	12.2	86	87.8	0.382
	Formula Fed	34	16.0	178	84.0	
Income	<10000	24	43.6	31	56.4	< 0.001
	11000–20000	16	23.2	53	76.2	
	> 20000	6	3.2	180	96.8	

Discussion

Worldwide the febrile seizures and iron deficiency anaemia are two very common diseases in children so as in our country. Iron insufficiency can cause many neurological symptoms e.g. behavioral changes, learning deficits and poor attention span in children. Hence it can also be related to other neurological disorders like febrile seizures in children.

The findings of this study regarding frequency of iron deficiency anaemia in children suffering with febrile seizures are found 14%, which are lower than a recent study, 1 revealed that iron deficiency anemia was 22% in children with febrile seizure. While in another study, it has concluded that its association is about 31.2%[11], which was also higher than reported in our study. On the other hand, a local study conducted in Faisalabad[10] showed that only 5.3% of the patients with febrile seizures were iron deficient while another study done in Rawalpindi showed a statistically significant relationship between febrile fits and low serum ferritin (P-Value 0.028).[12] These findings are also in contrast with our results. Sharif et al advocated that iron-deficiency anaemia increases the onset of febrile seizure.[13] Whereas Saha et al. disclosed that Serum Ferritin levels were lower in those patients significantly who have suffered with a first febrile seizure, as compared to in those patients who have febrile illness without convulsions.[14]

Khan et al. also stated in his study a strong association between iron-deficiency anemia in children and the febrile convulsions.[15] As compare to previously mentioned studies Lal and Hanif described no relationship between the two variables which are iron-deficiency anemia and occurrence of 1stfebrile convulsion in children less than 5 years of age.[16]

In another study conducted in Iran by Bidabadi and Mashouf. They reported that iron-deficiency anemia found to be less frequent in the patients who have febrile seizure than in controls.[17]

In view of the above findings and comparison, we have concluded that the iron deficiency anemia has association with febrile seizure in young children. However, our population is prone to this morbidity for 15% of the cases. The study from Faisalabad has shown a very low incidence which is not supported with our study.

Our study provides evidence based information of having iron deficiency anaemia with febrile seizures. This may guide for further strategies in management of febrile seizures like iron therapy. This study also gives an insight for further studies to determine association of iron deficiency anaemia with febrile seizures and its frequency after iron therapy.

Conclusion

We concluded that in young children who presented with febrile seizures in Services Hospital, the frequency of iron deficiency anemia was found to be 15.0%.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

M A S: Conceptualization of Project,

S K: Data Collection
S S: Literature Search
R O, M K M: Statistical Analysis
M A F: Drafting, Revision, Writing of Manuscript

Esculapio - Journal of Services Institute of Medical Sciences

Original Article

Is COVID-19 more Prevalent in Malaria Non-Endemic Countries than Malaria Endemic Countries?

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Abstract

objective: To highlight the immune system, producing an efficient response of interferon-g (IFN-g), caused by recurrent re-exposure to malaria in malaria endemic countries, inducing genetic polymorphisms in ACE2 and CD147.

Methods: Using WHO COVID-19 case reports, 20 of the most affected countries were selected and grouped in pairs with a comparable number of cases. 'Number of deaths in a country' was considered to be the indicator of severity of infection. Correlational tests were applied to determine the correlation between 'being malaria endemic or non-endemic' and 'severity of COVID infection (no. of deaths).

Results: There was a significant negative correlation between the extent of malaria being endemic in region and severity of COVID-19 infection (d=.483, p=0.03), (r=0.659, p=0.002) and (t=0.551, p=0.004) which shows that malaria endemicity negatively impacts COVID-19 fatality as there is essentially lesser fatality rate in malaria endemic countries as compared to malaria non-endemic ones with comparable number of cases.

Conclusions: Malaria endemic regions have lower death count as compared to malarial non-endemic regions. Reason being malaria modifying the key aspects of the immune system and receptors involved in the pathogenesis of COVID-19, resulting in better survival rate.

Keywords: COVID-19, malaria non-endemic countries, malaria endemic countries

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Introduction

From the initial mainstay preaching the efficacy of hydroxychloroquine on COVID-19 pathogenicity and mortality to its sudden withdrawal in the use of COVID, to its widely reported complications and anomalous presentations, COVID-19 has proved itself to be very unpredictable. Whilst sanitation and healthcare access has been stressed to be key in decreasing spread and mortality of the SARS virus, several world countries deprived of these necessities still report relatively the lowest number of cases and deaths. Inadequate testing and tracing has served as a blanket statement by many to explain this phenomenon, but it is far from detailed and adequate. Thus, we serve to scientifically explain this phenomenon in light of a hypothesis quickly gaining speed; is malaria endemicity in these 3rd world countries decreasing the prevalence and mortality of COVID-19?

Malaria is a disease that dates as far back as humans, with various researches attributing its longevity to the evolutionary characteristics the malarial parasite acquired alongside human.[1,2] Its ability to induce Angiotensin Converting Enzyme 2(ACE2) and Angiotensin Converting Enzyme 1(ACE1) gene polymorphisms allows for it to cause a diverse disease severity spectrum.[3] ACE2 specifically has also been implicated as binding site for the SARS-CoV spike (S) protein,[4] specifically, the S1 domain,[5] whereby it has been shown that a change in degree of binding site of SARS-CoV to ACE2 is associated with genetic polymorphism[4] which in turn influences SARS-CoV-2 susceptibility and COVID-

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19 disease outcome.[4,5]

Previous literature explains the low fatality rate in malaria-endemic countries and provides only limited statistical data.[6] Backed up by recent findings such as the ACE2 and CD147 molecules and by an immunological standpoint such as how a previous infection with malaria can attenuate the "cytokine storm".

Methods

Top 20 highly affected countries with highest COVID-19 cases were selected and labelled as malaria endemic or malaria non-endemic. This was done in accordance with WHO COVID case reports on 23rd of June 2020. Death count was taken the indicator for severity of virus in the region. Correlational tests were applied to determine the correlation between 'being malaria endemic or non-endemic' and 'severity of COVID infection and number of deaths.'

Statistical Analysis

The data was entered in SPSS and the correlation of subjects at hand was calculated using Spearman's, and Kendall's tau correlations. p-value < 0.01 was considered statistically significant.

Results

There was a significant negative correlation between the extent of malaria being endemic in region and severity of COVID-19 infection which shows that malaria endemicity negatively impacts COVID-19 fatality as there is essentially lesser fatality rate in malaria endemic countries as compared to malaria non-endemic ones with comparable number of cases.

The results from Spearman's, and Kendall's tau correlation (Table 2) show a negative correlation between the extent of malaria being endemic in a region and severity of COVID-19 infection (r=.659, p=0.002) and (t=.551, p=0.004). Despite having comparable count of reported cases, Malaria endemic countries have fewer number of deaths compared with malarial non-endemic countries.

Discussion

Our study shows a statistically negative correlation between the mortality rate due to COVID-19 and malaria-endemic countries. ACE2, the key receptor, follows a varied distribution in the body, having a dense concentration in some organs, but only a sparse concentration in others.[7] Acute Respiratory Distress Syndrome (ARDS) is one of the main determinants of mortality in COVID-19 patients,[8] and ACE2 has been postulated to be one of the main means of entry of the virus into the lungs.[9] The greater the degree of expression of ACE2 by cells, the more the facilitation of S-protein into the cell, and hence the greater the viral load.[10]

Table 1: Comparison of COVID Cases and Deaths in Malaria Endemic and Non Endemic Countries

Name of the country	Number of Cases	Number of deaths	Malaria Status
Italy	242,000	34868	Non-Endemic
Iran	240,000	11734	Endemic
Mexico	257,000	30912	Non-Endemic
Pakistan	232,000	4762	Endemic
France	167,000	29893	Non-Endemic
Saudi Arabia	110,000	1964	Endemic
Canada	106,000	8684	Non-Endemic
Bangladesh	166,000	2151	Endemic
Spain	251,000	28385	Non-Endemic
Peru	303,000	10589	Endemic
United Kingdom	285,000	44220	Non-Endemic
Chile	296,000	6308	Endemic
Belgium	61909	9771	Non-Endemic
Qatar	99799	133	Endemic
Germany	198,000	9088	Non-Endemic
South Africa	196,750	3,199	Endemic
USA	2930000	132000	Non-Endemic
India	697000	19693	Endemic
Russia	454000	10296	Non-Endemic
China	85306	4547	Endemic

Table 2: *Correlation between Malaria Endemicity and COVID-19 Fatality*

Test Applied	Correlation	p-value
Spearman's rho	-0.659	0.002
Kendall's Tau	-0.551	0.004

SARS-CoV-2 mediates its pathogenesis through the Renal Angiotensin Aldosterone System (RAAS),[11] specifically through Angiotensin II which promotes inflammation via Angiotensin Receptor 1 and Angiotensin Receptor 2.[12] However, Ang (1-7) produced, induces vasodilation, anti-apoptotic, and anti-inflammatory effects.[13] When the S-protein binds to the ACE2 receptor, ADAM metallopeptidase domain 17 (ADAM17) induces shedding and hence down-regulation of the ACE2 enzyme, inducing greater viral uptake.[14] This leads to increased levels of pro-inflammatory Angiotensin II but decreased levels of anti-inflammatory Ang (1-7). This also explains why ACE2 knockout mice experienced much greater deterioration in lung function, greater edema formation, markedly decreased expressions of ACE2 and elevated levels of Angiotensin II as compared to control mice.[15]

Elevated levels of Angiotensin II are suggested to disrupt the malarial parasite's cell membrane and thus reduce the accumulation of sporozoites in the salivary gland of the mosquito,[16] significantly decreasing the parasitemia observed in mice models[11], by activating mono-functional Interferon Gamma (IFN-g) producing

CD8+ T-cells[17] that spur partial protection and delay the progress of the disease.[18]

Malaria is adept at modifying the immune response to its benefit, inducing genetic polymorphisms in those structures of the parasite and host's tissues that protect the parasite, especially in endemic regions, where they impose a strong selective force on the human genome.[1,2,4] It has been noted that they can also induce polymorphisms that would benefit the host, including ACE2, and that this can influence the outcome of the SARS-CoV-2 infection, particularly in malaria-endemic countries.[6]

According to our hypothesis, if the SARS CoV-2 virus enters the cell and causes shedding of the ACE2 enzyme, people in malaria-endemic countries should experience a rapid progression towards complications and death. However, that is not the case and we explain how by introducing the role of cytokines in malaria and the "cytokine storm".

Significant positive correlation is observed between the levels of pro-inflammatory cytokines such as IFN-g, IL-6, IL-10[19] and disease severity, termed as "cytokine storm". Of these, IFN-g has been touted as one of the quarterbacks of the immune system's response to the virus.[20] It is not the gross quantity, but rather the efficiency with which IFN-g is produced that determines the prognosis of the disease.[20]

This is best demonstrated in a study where those who were able to mount a quick and robust IFN-g response were only associated with mild incidences,[21] whereas those with severe malaria were found to have much higher systemic levels of IFN-g.[21] It has been postulated that in the 2nd or 3rd exposure to malaria cross-reactive primed T-cells are still 'practicing' and produce gross copious amounts of IFN-g. However, in the first exposure, very little IFN-g is produced, whereas repeated exposure has 'trained' T-cells to launch a more efficient and well-regulated immune response, and this is associated with the best prognosis[22]. This demonstrates the same phenomenon observed in COVID-19; it is not the amount of IFN-γ produced during an infection but rather the timing, efficiency, and regulation of production of IFN-γ that is associated with survival.

Another common target receptor for both Malaria and COVID-19 is the recently known receptor CD-147 (EMMPERIN). CD-147 is expressed on several immune cells where it causes induction of chemotactic cytokines (TNF-alpha, IL-10, IL-6), causes MMP2, IL-9 induction, production of Interferon gamma (IL-18), T-cell activation, proliferation, invasion, adhesion and energy activation.[23] Interferons released by lymphocytes is normal immune response to infection by multiple strains of malaria, and that these same interferons have both in vivo and in vitro effects against coronaviruses responsible for SARS, MERS, and COVID-19.[24] Repeated exposure to malarial infections induces the development of persisting neutralizing antibodies that neutralize a broad profile of merozoite antigens.[24] CD 147 as a route of entry suggests a possible mechanism of action for this protection and also provides a basis for anti-CD 147 drugs as a treatment option for COVID-19.[25]

Thus, extrapolating our findings to COVID-19, we hypothesize that the constant re-exposure to malaria in malaria-endemic regions has 'evolved' the innate immune system, which chooses to launch an efficient attack, producing IFN-g in right amounts at the beginning, and then choosing to decrease the production of IFN-g during later stages. The ability to do so significantly decreases progression of disease and mortality due to COVID-19 in malaria-endemic regions.

Limitations

Our study has limitations, though. Inaccurate reporting of the data might lead to the falsification of results. Experimental data is required to justify the hypothesis.

Conclusion

Malarial endemic regions have less death count as compared to malarial non-endemic regions. There exists a strong negative correlation between SARS-CoV-2 and malaria endemic regions, and we have presented hypotheses in line with current research on SARS-CoV-2 as well as previous SARS infections. We believe that malaria has conferred a protection against COVID-19, by having induced polymorphisms in the ACE2 molecule, the main molecule in the pathogenesis of SARS-CoV-2, and by modifying the IFN-g response to effectively respond against SARS-CoV-2 infection.

Conflict of Interest *None*

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Authors Contribution

ARA: Conceptualization of Project,

IB, FI: Data Collection, Revision, Writing of Manuscript
RKA: Literature Search
AT, AA: Statistical Analysis, Drafting

Esculapio - Journal of Services Institute of Medical Sciences

Original Article

Comparison Between the Efficacy Rison of between Topical 2% Tranexamic Acid Versus 2% Hydroquinone in the Management of Melasma

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Abstract

Objective: To compare the efficacy of topical 2% Tranexamic acid versus 2% hydroquinone in the treatment of Melasma.

Methods: This is randomized controlled study done from 01 June 2020 to 31 December 2020 in the Department of Dermatology, Lahore general hospital, Lahore.

Total 120 patients of both genders, aged 19-45 years were taken. Baseline MASI scoring was used to assess the severity of melasma and effectiveness of treatment. The patients were divided into two equal groups. Group A was given topical 2% Tranexamic acid (TA) and group B 2% hydroquinone (HQ). Both groups advised to avoid sun exposure and use sun block. After 12 weeks of therapy, clinical inspection and MASI scoring was done to observe the effect of both drugs and results were recorded. SPSS 20 was used for data analysis.

Results: Total 120 patients of mean age 30.01±6.26 years were enrolled. Females were 56 (46.7%) and males were 64 (53.3%). Baseline MASI score was 24.50±4.14, in TA group was 23.85±3.90 and HQ group was 24.65±4.36. TheCombinely collective post treatment MASI score was 13.40, with group A was 11.70 and with group B was 15.11. Efficacy was achieved in 59 (49.2%) and not achieved in the 61 (50.8%) cases. On comparison of groups with respect to efficacy, 43 (71.7%) achieved efficacy in TA and 16 (26.7%) in HQ group with p-value <0.05.

Conclusion: Tranexamic acid is effective for the management of melasma as compared to the Hydroquinone.

Key words: Tranexamic acid 2%, Hydroquinone 2%, melasma, melasma area and severity index (MASI)

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Introduction

Melasma is a common dermatological problem worldwide. It develops frequently on face as brown or grey- brown patches. Majority of individuals acquire this discoloration on their cheeks, forehead, nose and the area between the upper lips and nose. Neck and forearms also prone to develop melasma because of excessive sun exposure. [1]

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There are 2 common patterns of melasma on face, one is present on central regions of face like forehead, upper lips, and central part of chin and other is peripheral part that involves the cheek bone area. The 3rd less common pattern is involving the jaw line.[2]

Brown discoloration in melasma is appeared due to increased activity of melanocytes present in epidermis. The stimulation of melanocyte is mostly caused by ultra-violet rays. Melasma affects both males and females of all races particularly the Asian population and people of Hispanic origin live in tropical region. It is frequently developed in females of reproductive age group but menopausal age group also affected commonly. The women during pregnancy are at increased risk of getting this discoloration. The onset of melasma is between 26-55 years in women. Men are also affected by this problem but less than women.[3]

The quality of life is also affected by melasma and patient develop anxiety and depression after getting

this ugly discoloration on their face. The psychological disease burden increased when compared with patients without melasma.[4] The exact incidence of melasma in Pakistan is not known because no such study was conducted up to now. The incidence of melasma worldwide is around 1-50% and in Pakistan the prevalence of melasma is approximately 45% especially in pregnant women.[5] The histopathological changes seen in patients of melasma is increase melanocytes epidermally. The total number of melanocytes are not markedly increased but they became hypertrophied.[6]

Vascular factors are also contributing in melasma. Studied discovered that vascular endothelial growth factor (VEGF) was intense in hyperpigmented area. Recently discovered other factors that are involved in disease process like fibroblast growth factors, TGF-B, nitric oxide synthase inducible type (iNOS) and some modulatory genes that control the WNT pathway. The significant knowledge of these factors could help in treatment modalities and provide platform for discovering newer drugs.[7] Epidemiologically the studies on melasma in men are very few. According to one study, the melasma in men is less than the females but quality of life affects more in males than females. Majority of the males develop discoloration on face after the age of 30 years.[8] Histologically findings are similar with clinical patterns observed in men. In accordance with these similarities, female hormones may not be the sole responsible factor for melasma.[9]

The low incidence of melasma in men can be due to testosterone that shows some resistance in the development of melasma. Other factors also play a valuable role in melasma like use of some vegetable oil and the drugs used to treat prostate cancer i.e diethylstilboestrol.[10] Mustard oil used for hair growth and moisturizer seems to be one of the causative factors of melasma in males.[11] The mechanism behind melasma is very complicated and different factors in synergistic manner play significant role like genetic tendency, ultraviolet rays, hormones and some medicines. The onset of melasma starts and more obvious after sun exposure, that reflects the strong causative association.

In females, pregnancy is one of the important triggering factors in melasma because some hormones like estrogen, progesterone and Melanocyte-Stimulating Hormone (MSH) are raised in pregnancy. As the pregnancy goes on, the level of these hormones increased that reflect the appearance of melasma in third trimester commonly.[12]

These hyper pigmentary disorders are so common and challenging for dermatologist as they are linked with emotional and psychological outcomes. Some patients are very much conscious about their beauty that seldom they develop suicidal thoughts that can be difficult to deal and treat by psychiatrists sometimes.[13]

Melasma is mainly treated by medications but sometimes procedures are required to deal with this problem. Diverse treatment options are running since many decade ranges from simple avoidance to invasive procedures.

Topical application of medicine is the first line treatment. HQ is the most frequently prescribed medicine in the treatment of melasma. HQ impedes the switching of DOPA to melanin by inhibiting the tyrosinase enzyme that ultimately cause death of melanocytes. Worldwide, HQ is one of the popular drugs used for treating hyper pigmentation and considered a gold standard for managing melasma. HQ is also prepared in combination with some other medicines like steroids, retinoids, glycolic acid and sun blocks for better results. Alternatively, Tranexamic acid is an artificial and synthetic based lysine product that inhibit the prostaglandin production thus inhibits the tyrosine enzyme function.[14]

The purpose of this study is to solve the arguments and discrepancy about the effectiveness of HQ and TA in the management of melasma. We have searched the studies that is done for direct comparison between two drugs in the treatment of melasma, but unfortunately no local study was found.

Objective

To compare the efficacy of topical 2% Tranexamic acid versus 2% hydroquinone in the management of Melasma.

Methods

This study was done in dermatology department of LGH in 6 months of duration from 01-June 2020 to 31-December 2020. The study design is randomized controlled trail with sample size of 120 cases (60 cases in both groups). The patients of both genders between 18 to 45 years age, patients of Fitzpatrick skin type III to V, patients diagnosed with melasma by clinical definition with baseline MASI score 6.5 to 32 were included in this study. Patients diagnosed with different non neoplastic dermatological condition like SLE and discoid lupus, pregnant and nursing women with melasma and patients who were already taking medicines for melasma or any medicine for other disease were excluded.

Ethical approval letter from ethical committee of hospital was taken primarily. All the patients of melasma were registered after their informed consent. The demographic information was recorded like age, gender, contact numbers and address. Baseline MASI score was used to assess the severity of melasma as well as efficacy of treatment. The patients were separated in

two group (60 each) labelled with group A and B. Topical 2% tranexamic acid (TA) was given to group A and 2% hydroquinone (HQ) was given to group B.
Group A and B were guided to avoid extreme sun light and simultaneously use sun screen SPF 60. After 12 weeks of continuous treatment the clinical examination was done with MASI scoring to establish the positive effects of both drugs.
The software SPSS 20 was used for analysis of data. Age, baseline and post treatment MASI score was recorded as quantitative data shown with mean and standard deviation. Gender and effectiveness of drugs were recorded as qualitative data and explained by percentages and frequency. Chi square test was applied to compare the efficacy in both treatment groups. A p-value <0.05 was taken significant. Data was stratified for gender and age . Post treatment chi square test was applied keeping p-value< 0.05 as significant.

Results

Total 120 patients were enrolled in this study with mean age of 30.01±6.26 years. The mean age group with gender distribution is shown in table 1. Before treatment the baseline MASI score overall was 24.50± 4.14, with tranexamic acid was 23.85±3.90 and with hydroquinone group was 24.65±4.36. Collectively post treatment MASI score was 13.40, with group A was 11.70 and with group B was 15.11. The overall effectiveness with comparison was shown in table 2 with significant p value of <0.05.
On analysis it was found that age has momentous effect on the effectiveness of therapy. The age group between 19-30 years show positive results in 22 (66.7%) cases and in age group of more than 31 years, 21(77.8%) show notably significant response. Similarly, gender difference was also considerably noted (Table 1)

Table 1: *Distribution of the Gender with Age in the study Population (n=120)*

Groups	Age range (18-45 years) Mean±SD	Male, frequency (%)	Female, frequency (%)
Group-A (n=60)	29.73±6.1	33(55%)	27(45%)
Group-B (n=60)	30.30±5.2	31(51.7%)	29(48.3%)
Total (n=120)	30.01±6.6	64(53.33%)	56(46.66%)

Table 2: *Comparison of Efficacy by MASI Score in the Treatment Groups A and B (n=120)*

Efficacy of treatment	2%Tranexamic acid	2% Hydrquinone	Both
Yes	43 (71.66%)	16(26.66%)	59(49.16%)
No	17 (28.33%)	44(73.33%)	61(50.8%)

P-value = <0.002

Discussion

Melasma is one of the most frequently encountered problem faced by dermatologist. The treatment of melasma remains a big challenge for decades and need long-time therapies. Topical treatment remains the basic and mainstay in the management of melasma. Many studies provided attention towards the positive effects of oral as well as topical use of Tranexamic acid in melasma. The mean age of patient in our study was 30.01±6.26 years, this is in similar to study done by Hassan et al.15 Most of the patients in our study were male (53.33%), this is in contrast with the study conducted by Desale et al.[16]

This study found be in favor of topical use of 2% TA, this is compared with the study done by Kim et al, that found mean MASI was significantly improved after topical TA therapy in 22 patients out of 23.[17]

In this study patients of Fitzpatrick skin type III to V were taken, this is in line with the study done by Amir et al.[18] In our study the post treatment MASI score noticed in group A was 11.70 and in group B was 13.11, reduced to more than 50% and less than 50 % respectively. In contrast to study done by Janney et al in which they noticed baseline MASI was 12.39+3.34 and 11.63+ 3.72 in TA and HQ group respectively. The reduction of MASI was noticed 27% and 26.7% in the TA and HQ group respectively after 12 weeks of treatment.[19]

According to the study done in Nepal by Karn et al, the results of both oral tranexamic acid and topical hydroquinone was compared to group used topical hydroquinone alone. The study was done in 260 patients that were divided equally into two groups and taken treatment for 12 weeks. The significant results assessed by fall in MASI score were noted by the group who have taken both the drugs as compared to hydroquinone alone at 8th week and 12th week. In our study MASI score was fall significantly in group A patients in contrast to group B patients who were using hydroquinone.[20]

In our study the male gender indicates predominancy (53.33%) that is reflected in the better treatment response, in contrast to study conducted in Pakistan by Aslam A et al that shows female predominancy (85%).[21]

The effectiveness of TA in our study is more favorable than HQ, augmented and comparable to study done by El-Husseiny et al.[22]

Some side effects were noted with the use of HQ. The adverse effects of hydroquinone are dose and time dependent, in which most common is the irritation.[25] Erythema and mild allergic reactions were also noted in our study but no adverse effects were seen with the use of TA.

One important limitation of our study that we did not

follow up the patients after 12 weeks of therapy to observe any recurrence of pigmentation.

Conclusion

As a final point, it is supposed to be concluded that topical application of 2% tranexamic acid is a recent and experienced medical treatment in the management of melasma. It gives quick and promising results in both genders. There is no such adverse effect seen that need to stop its use.

Conflict of Interest None

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Authors Contribution

Z S, A S: Conceptualization of Project,

M S, A S: Data Collection, Revision, Writing of Manuscript
S M: Literature Search
M S: Statistical Analysis, Drafting,

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Original Article

Association of Placental Location with Estimated Fetal Weight and Umbilical Artery Doppler Indices in Pakistani Cohort

Khoala Riaz, Maria Khaliq, Anum Yousaf, Iram Iqbal, Amna Khalid, Riffat Raja

Abstract

Objective: To see relationship of placental location with estimated fetal weight and umbilical artery S/D in our population.

Methods: A total of 400 pregnant women with singleton pregnancy of age 20 to 38 years were included. Pregnant females with co-morbidities and twin pregnancy were excluded. Placental location, estimated fetal weight and umbilical artery S/D were calculated and any association between them was evaluated.

Results: In Pakistani population, most common placental location was posterior (38%) followed by anterior(31%). Lateral placental site was least common(12%) and fundal placenta comprises only(19%) .Though there is no statistically significant difference but umbilical artery S/D was highest for fundal placenta and lowest for anterior placenta. The estimated fetal weight was highest for fundal placenta in ninth month of pregnancy and highest for anterior placenta in eight month without any statistically significant association.

Conclusion: There is no statistically significant relationship of placental location in uterus with estimated fetal weight and umbilical artery S/D.

Keywords: estimated fetal weight, placental location.

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Introduction

Placenta is the most important organ for developing fetus and is considered as largest and earliest developing fetal part.[1] It is attached to uterine wall on one side and with fetus through umbilical cord. It not only serves as liver, kidney and gut of fetus but also act as important endocrine organ. It is a medium through which important nutrients and gases passes from mother to the fetus and waste material passes vice versa either by diffusion or active transport.[2]

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In second trimester, as a part of antenatal care, at least one antenatal ultrasound is advised by obstetricians to get accurate information for optimization of better pregnancy outcome. One essential component of this scan is information about placental location. Placenta can be located in upper uterine segment or lower. The term previa is used when placenta either covers the internal orifice of cervix uteri or lower placental margin ends within 2 cm of the internal os. Placental location in upper uterine segment can be classified in four types depending on wall to which it is attached, namely anterior (attached to frontal/anterior wall), posterior (attached to back wall), fundal(attached to top wall) and lateral (attached to right or left walls).[3] Best imaging modality for assessment of placenta is ultrasound on which it is seen in 10th week of gestation as a thin echogenic rim.[4]

Ultrasound evaluation of estimated fetal weight is very important factor not only in antenatal management and post natal care of the baby but also in guiding time and mode of delivery[5]. Fetal weight depends on many

factors including maternal health, nutrition and socio-economic status, smoking, ethnicity, gestational age, parity and paternal height. Normal healthy placenta is the key in establishing the feto-maternal circulation and thus healthy fetus.

Uterus is mostly supplied by uterine artery however blood distribution in uterine walls is not uniform. During pregnancy placental implantation site may have some significant role in determining placental blood flow. Placental implantation site association with antepartum hemorrhage, IUGR, premature rupture of membranes, preterm labour[6], fetal malposition, pre-eclampsia, fetal sex and pregnancy outcome has been described previously; however, no clear data is available explaining relationship of fetal weight and umbilical artery S/D with placental location in Pakistani population. So this study was carried out in a teaching hospital in Pakistan to establish if there is any relationship of placental location with umbilical artery S/D and estimated fetal weight, so that it can be used as an important predictor of pregnancy complication like pre-eclampsia and IUGR .S/D is the ratio between peak systolic velocity and diastolic velocity of umbilical artery and is used as an important indicator of fetomaternal circulation by measuring vascular resistance. Its normal value drops from 3.9 to 2.0 during 20th to 40th week.

Methods

This prospective cohort study was carried out at department of Radiology, Benazir Bhutto Hospital, Rawalpindi from 1st Sep, 2020 to 1st Dec,2020. Using non-probability purposive sampling 400 pregnant women of age 20-38 years with singleton pregnancy and presenting in third trimester were included after ethical approval of the study from the ethical review board of the Medical College. Patients with co morbidity and in first & second trimester were excluded. After taking informed consent, ultrasound was done by Toshiba Doppler ultrasound machine using 3.5 MHZ curvilinear transducer. Ultrasound was performed by placing the transducer in epigastrium and moving down to suprapubic region. Same procedure was repeated on both sides and placental location was interpreted as anterior, posterior, fundal, lateral and previa . Ultrasound and Doppler studies were carried out by a qualified Radiologists with atleast three years of post-fellowship experience and a post graduate trainee. The fetal parameters used to determine Estimated fetal weight were BPD(biparietal diameter), AC (Abdominal circumference) and FL(femur length). Hadlocks formula was used .The grey scale findings of ultrasound were noted and interpreted collectively by the radiologist and placental location and estimated fetal weight were tabulated.

Gathered data was analyzed through computer software SPSS 23.0. Placental location/implantation site was categorical variable and estimated fetal weight (EFW) and Umbilical artery S/D were continuous variables. Results were expressed as Mean±S.D. and percentages for continuous variable and categorical data respectively. Categorical variables were tested by one way Anova test. P value > 0.05 was considered statistically significant.

Results

Age range in this study was from 20-38 years with mean age of 29.35±3.44 years.

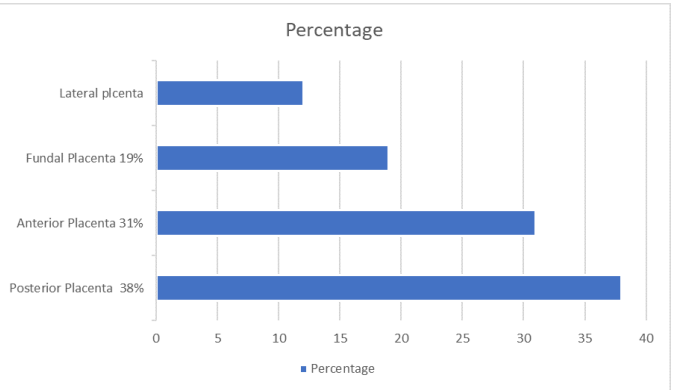

Figure: *Showing Prevalence of Different Categories of Placental Location in Pakistani Population*

All the patients were subjected to USG. 398 USG showed placenta in upper uterine segment and only 2 showed placenta terminating less than 2cm from internal os i-e previa. In our study, most common placental implantation site was posterior(38%) followed by anterior (31%). 19% placenta were fundal and lateral is the least common placental implantation site(12%). This is shown in graph I.

Association of estimated fetal weight calculated by USG with placental location was evaluated by dividing the sample population in two groups according to gestation age Table I. In first group(gestational age 33 weeks to 36 weeks), estimated fetal weight was highest for anterior placental location (2877±175) and lowest for fundal location (2747±139). In second group (gestational age 36weeks to 40 weeks), opposite findings

were observed, with highest EFW in fundal placental location (3538±251)and lowest in posterior placental site(3437±284).The difference in estimated fetal weight according to placental implantation site is not statistically significant as p-value is >0.05. Doppler ultrasound also showed that S/D of umbilical artery is highest for fundal placenta (2.273±0.312) and lowest for anterior placenta (2.219±0.296). However, placental implantation site doesnot have any statistically significant effect on S/D of umbilical artery as p-value is >0.05.This is summarize in Table II.

Discussion

Placental attachment site on the uterus is of utmost importance especially for determining safe mode of delivery (either vaginal or through C-Section), for diagnosis of placenta previa and for Placental morbid adherence probability.

Sufficient literature is available regarding placental location association with pre-eclampsia, preterm labour, antepartum hemorrhage, pregnancy outcome, fetal malposition, fetal gender; however, no data is available evaluating implication of placental implantation site on fetal birth weight and umbilical artery S/D especially in Pakistani population. Effective fetal weight is an important factor in deciding pregnancy outcome, newborn health, obstetric planning and management.[7]

Table 1: *Distribution of Effective Fetal Weight (EFW) (Means±SD)in Two Gestational Age Groups for Different Placental Locations.*

Gestational age	EFW in Posterior placenta (grams) Mean±SD	EFW in anterior placenta (grams) Means±SD	EFW in Fundal placenta (grams) Means±SD	EFW in lateral placenta (grams) Means±SD	p-value
33 to 36 weeks	2810±186	2877±175	2747±139	2824±228	0.322
36weeks to 40 weeks	3437±284	3491±290	3538±251	3448±312	0.854

Table 2: *Distribution of Umbilical Artery S/D (Means±SD) for different Types of Placental Locations.*

Gestational age	Umbilical artery S/D in Posterior placenta Mean±SD	Umbilical artery S/D in anterior placenta Means±SD	Umbilical artery S/D in Fundal placenta Means±SD	Umbilical artery S/D in lateral placenta Means±SD	p-value
33 to 40 weeks	2.257±0.393	2.219±0.296	2.273±0.312	2.250±0.355	0.950

In our study, only two patients out of 400 had placenta previa. This result is in line with many previous studies like one study conducted by Audrey Merriam and Mary E. D Alton8 .The most common implantation site of placenta in our study is posterior followed by anterior. Lateral uterine walls are least common site for placental implantation according to our results. These results are in concordance with a study carried out by Granfors M et al. which also showed that anterior and posterior locations are most common placental attachment sites (though anterior more common than posterior which is contradictory to our study) followed by fundal location. In this study like ours, lateral implantation site was least common.[9]

According to our results, there is no association between placental location site on uterus with estimated fetal weight. Mumal Nagwani et al. also found out that there is no link between placental location and estimated fetal weight between 33 to 40weeks, however their study showed significant association between placental site and fetal weight in early third trimester[10]. In our study, estimated fetal weight in anterior placentation is slightly higher near term. This is in accordance with a study conducted by Duran Erdulo M et al.[11]

Similarly, in a local study in Saudia Arabia conducted by Shumaila Z, they did not observe any significant influence of placental location on fetal weight[12]. Lin D et al. carried out a retrospective cohort study in diamniotic dichorionic twins to see the relationship of placental implantation site on fetal birth weight and the outcome of their study was also similar to our study suggesting no association of these two factors[13].

According to our results, Umbilical artery S/D has no association with fetal birth weight. This is in concordance to a study carried out by Dorun Erdulo et al.[11] Similar findings were also reported by a study carried out by Al-Sheikh et al.[14]

Few limitations of this study includes small sample size and study of only one Doppler parameter. The explanatory power of the study can be improved by adding PI and RI of umbilical artery and Doppler indices of other vessels like uterine artery.

Conclusion

This study concluded that in Pakistani population, upper segment placenta is more common than placenta previa.

The most common placental implantation site in our population is posterior and least common is lateral. This study also showed that placental implantation site has no statistically significant association with estimated fetal weight and umbilical artery S/D. So, placental implantation site other than placenta previa should not be used as a predictor of poor pregnancy outcome and lower birth weight babies. The role of placental localization by ultrasound is only to rule out possibility of placenta previa and morbid adherence of placenta.

Conflict of Interest: None

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Authors Contribution

K R, M K: Conceptualization of Project,
K R, M K, A U, R R: Data Collection
M K, A U, R R: Literature Search
A U, I I, A K: Statistical Analysis
I I, A K, R R: Drafting, Revision
K R, I I, A K: Writing of Manuscript

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