Editorial:

PAKISTAN IN ERA OF EXTENSIVE DRUG RESISTANCE ENTERIC FEVER.

Tariq Waseem

Enteric fever which is also known as typhoid fever is caused by gram-negative bacteria salmonella enteric serovar Typhi bacteria (S.Typhi), Even today enteric fever remains a global health problem and results more than 21. Approximately 6 million cases and least 250,000 deaths annually.[1] The majority of these cases and deaths (80%) occur in Asia; the remaining 20% occur in Africa and Latin America.

Enteric fever spreads through oro-fecal route by consuming contaminated food or water. Poor sanitation and poor hygienic conditions remain a major risk factor for its spread. Travelers to and from the developing world are at increased risk. At the start of 2nd millennium, Enteric fever was responsible for 21.7 million illnesses and 217,000 deaths. The majority of deaths occur in young age group of 5 to 19 years. The number of deaths attributed to enteric fever was reduced to 161,000 in 2013, as compared to 181,000 in year 1990.[2] Improvement in water sanitation and food handling in developed and industrialized countries, have largely reduced the number of cases, but situation in underdeveloped and developing nations remains alarming. Asia and Africa have the highest morbidity and mortality due to enteric fever poses the biggest challenge. A lack of access to clean drinking water, proper hygienic sanitation systems, and proper health-care facilities contribute to the spread of enteric fever in these countries.[3]

The history of typhoid fever is quite interesting. In 430 BC, an epidemic of typhoid fever emerged first time in Athens & killed their leader Pericles.[4]

Professor Medicine, Akhtar Saeed Trust Hospital, Lahore.

A study published in 2018 suggests that the epidemics that struck the Mexican areas in the year 1545 and 1576 and was responsible for an estimated 7 to 17 million deaths, was actually typhoid fever.[5] The 9th US President William Henry Harrison did not die of pneumonia as was thought but of enteric fever. Similarly 12th US President Zachary Taylor also died of enteric fever due to the poor sanitary conditions in Washington, DC.[6] In year 1907, Mary Mallon is also known as Typhoid Mary the most notorious carrier of enteric fever became the first carrier in the United States. She was a cook in New York and was responsible for 53 cases and three deaths.[7] In 2004–2005 an outbreak in Democratic Republic of Congo resulted in more than 42,000 cases and 214 deaths.[1]

Treatment of enteric fever revolutionized with the discovery of Chloramphenicol in 1948 and Cotrimoxazole and Ampicillin later on, but resistance to these drugs was soon reported. Rampant and indiscriminate use of these drugs was mainly responsible for emergence of resistant bacterial strains. chloramphenicol-resistant was reported from United Kingdom. However, it was not until year 1972 when chloramphenicol-resistance became a significant issue, with major outbreaks reported in Mexico in 1972, India in 1972, Vietnam in 1973 and Korea in 1977. These strains when tested were also found to be resistant to ampicillin. Co-trimoxazole was the only effective drug in the treatment of these resistant strains until the year 1975.In 1975 Co-trimoxazole was also reported in France as a resistant drug towards enteric fever. By the end of 1980s, the strains of S.Typhi that were resistant to all three first-line drugs were present.[8]

Multidrug-resistant enteric fever (MDREF) is defined as an enteric fever that is caused by S.Typhi and its strains which are resistant to all of the three first-line drugs that are recommended for treatment, i.e., chloramphenicol, ampicillin, and co-trimoxazole.

Then comes the Era of Fluoroquinolones, which emerged as the treatment of choice. The widespread use of 2nd generation of fluoroquinolones i.e. ciprofloxacin and ofloxacin-levofloxacin has now led to the reduced susceptibility of organism across the Indian subcontinent. Complete fluoroquinolone resistance, that includes the resistance to the newer generation fluoroquinolone gatifloxacin, emerged after 2010 and is now associated with treatment failures and prolonged disease.[9]

Most centers in South America, India, Pakistan, Bangladesh, Thailand, or Vietnam have switched from fluoroquinolones to third-generation cephalosporins as first-line treatment for enteric fever. For these regions, the recommendations are to use ceftriaxone as a first-line treatment. Azithromycin has recently been recommended for treating resistant typhoid in populations that are both fluoroquinolone and ceftriaxone resistant.[8] In Sindh Pakistan between the years 2016 and 2017clones of S.Typhi resistant to all first-line drugs and fluoroquinolones were reported, classified as extensively drug-resistant (XDR) Typhoid. Frequent air travel transfers these strains from one country to another within no time. In year 2018 two alerts have been triggered as XDR enteric fever cases are reported in United Kingdom and United States of America among the travelers who were returning from Pakistan.[10] Similarly another XDR case of enteric fever in Denmark was reported in 2019, April in traveler who was 15 weeks pregnant woman returning from Karachi, Pakistan. The women were treated with Cefixime for 1 week than with Ceftriaxone 2g once daily but due to deteriorated condition the treatment was changed to Azithromycin 500 mg daily and Meropenum 1g thrice daily, which later resulted in clinical improvement and decreasing C-Reactive Protein (CRP). The patient was discharged on the 15th day with oral Azithromycin with healthy fetus.[11]

Extensively drug-resistant (XDR) enteric fever is rapidly spreading in Pakistan, increasing the fears of antibiotic failure at the international level.[12] Experts consider that Pakistan's unfathomable sewage and water systems along with low vaccination rates and heavily populated cities are the main causes of the spread of extensively drug-resistant (XDR)enteric fever. In the period between 2016 and 2017, health authorities in Pakistan have detected more than 800 cases of extensively drug-resistant (XDR) enteric fever only in the city of Hyderabad.[13]

The outbreak of extensively drug-resistant (XDR) enteric fever should be considered as an alarming signal that the world is gradually moving towards a pre-antibiotic age because of unrestricted overuse of antibiotics. This has become a genuine concern in developing countries like Pakistan, where antimicrobial surveillance is in worse shape and there is an urgent need for strengthening the system. In this aspect both governmental and non-governmental organizations need to make an extensive program on promoting vaccination campaigns and adopting healthy hygienic eating and living habits. Also it is important to discourage irrational and over the counter use of antibiotics to prevent the mortality and morbidity that is linked with escalating antibiotic resistance.

REFERENCES

1. Crump JA, Mintz ED. Global trends in typhoid and paratyphoid fever. Clinical infectious diseases. 2010 Jan 15;50(2):241-6.
2. Crump JA, Sjölund-Karlsson M, Gordon MA, Parry CM. Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance, and antimicrobial management of invasive Salmonella

infections. Clinical microbiology reviews. 2015 Oct 1;28(4):901-37.
3. Khan MI, Pach 3rd A, Khan GM, Bajracharya D, Sahastrabuddhe S, Bhutta W, Tahir R, Soofi S, Thapa CB, Joshi N, Puri MK. Typhoid vaccine introduction: An evidence-based pilot implementation project in Nepal and Pakistan. Vaccine. 2015 Jun 19;33:C62-7.
4. Papagrigorakis MJ, Yapijakis C, Synodinos PN, Baziotopoulou-Valavani E. DNA examination of ancient dental pulp incriminates typhoid fever as a probable cause of the Plague of Athens. International Journal of Infectious Diseases. 2006 May 1;10(3):206-14..
5. Acuña-Soto R, Stahle DW, Cleaveland MK, Therrell MD. Megadrought and megadeath in 16th century Mexico. Emerging infectious diseases. 2002 Apr;8(4):360.
6. Bray RS. Armies of pestilence: the impact of disease on history. James Clarke & Co.; 2004.
7. Bartoletti SC. Terrible Typhoid Mary: A true story of the deadliest cook in America. Houghton Mifflin Harcourt; 2015 Aug 4.
8. Parry CM, Beeching NJ. Treatment of enteric fever. BMJ 2009; 338 doi: https://doi.org/10.1136/bmj.b1159
9. Effa EE, Lassi ZS, Critchley JA, Garner P, Sinclair D, Olliaro PL, Bhutta ZA. Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). Cochrane Database of Systematic Reviews. 2011(10)..
10. Saleem Z, Hassali MA. Travellers take heed: Outbreak of extensively drug resistant (XDR) typhoid fever in Pakistan and a warning from the US CDC. Travel medicine and infectious disease. 2019;27:127.
11. Engsbro AL, Goldschmidt MI, Jespersen HR." Ceftriaxone resistant Salmonella enterica serotype in pregnant traveler from Pakistan to Denmark, 2019".
12. Dalton J Typhoid superbug in Pakistan raises fears of global antibiotic failure. Independent. April 2018 01:38
13. Ahmad M. Pakistan is racing to combat the world's first extensively drug-resistant typhoid outbreak. Sci Am, March 14, 2018. https://www. scientificamerican.com/article/pakistan-isracing-to-combat-the-worlds-first-extensivelydrug-resistant-typhoid-outbreak (accessed May 7, 2018).

Original Article

CLINICAL AND CYTOLOGICAL EVALUATION OF ORAL MUCOSAL LESIONS IN PAN-CHEWERS FROM LAHORE, PAKISTAN

Sadaf Waris, Atika Masood, Rabia Safdar, Khurshid Ali, Abdur Rehman, Nadia Wali.

ABSTRACT

Objective: The current study was performed to asses demographic, clinical and cyto-morphological features of oral mucosa in pan chewers.

Methods: This was a cross-sectional, survey. After taking relevant history and informed consent, a clinical examination was performed on 300 pan users from Lahore city. Cytological smears were obtained to be stained with Haematoxylin and Eosin, Giemsa and Pap's stain. All the smears were examined under light microscope to evaluate cyto-morphological changes. Data were analyzed with the help of SPSS.

Results: The average age for all subjects was 32.28±0.59 and 95% were males. The majority were from poor social background and some of them gave history of smoking and alcohol etc. Many had discolored and sensitive teeth, bleeding gums and painful oral lesions. The mean duration of pan chewing was 11.47±0.39 years and majority of subjects used to chew 1-5 pans /day. On naked eye examination of oral cavity, leukoplakia, erythroleukoplakia, oral submucous fibrosis, erythroplakia, and growth were seen in 8.7%, 2.3%, 1.7%, 1%, and 1% subjects respectively. On cytological examination epithelial dysplasia, oral squamous cell carcinoma, keratosis, inflammation, bacterial and candidal loads were observed in 57.7%, 1%, 54.3%, 74.7%, 48.7%, and 7.7% subjects respectively.

Conclusion: Poor orodental hygiene, inflammatory conditions, pre-malignant lesions like leukoplakia, erythroplakia, epithelial dysplasia and malignancy of oral mucosa were alarmingly common in pan chewers from Lahore, Pakistan who belonged to the poor socioeconomic background and do not seek medical advice.

Key Words: Oral Mucosa, Leukoplakia, Keratosis, Oral submucous fibrosis

INTRODUCTION

Pan or betel quid chewing is widespread in many parts of Asia and the migrants from this area have transferred this abuse from Asia to all parts of the world.[1] It has been estimated that 10% of world's population (600 million) is addicted to betel quid chewing across the globe.[2] People around world are quite familiar with the name of betel quid'.Unfortunately, inadequate attention is given to its varied components.The key ingredients of 'betel quid' (pan – a term more known to Southeast Asians) are betel leaf, areca nut, slaked lime, and tobacco.[3]

Department of Morbid Anatomy and Histopathology, University of Health Sciences, Lahore, Pakistan

Additional constituents such as cardamom, aniseed, sweeteners (coconut, dried dates), and essences (rose petals, mint, menthol) are added to enhance its flavor.[4] In Pakistan, pans are readily available at 'pan stalls'. Pan sellers often apply a mixture of slaked lime, areca nut and a variety of other flavoring ingredients to a betel leaf and wrap into a rough triangle shape 'pan'.[5]

Consumption of betel quid and a number of its constituents like areca nut and tobacco are detrimental to oral mucosa as they contain numerous toxic compounds, heavy metals and other hazardous by-products including reactive oxygen species which are established mutagens and carcinogens.[6,7] A large number of lesions like leukoplakia, erythroplakia, oral submucosal fibrosis, epithelial dysplasia, and oral cancer are caused by habitual pan chewing.[4] This study was conducted to describe the demographic

attributes of chronic pan users and to demonstrate the variety of abnormalities found in them on clinical examination and cytological evaluation of their buccal mucosa.

METHODS

This was a cross-sectional descriptive type of study, conducted in Lahore city. The cytological evaluation of oral mucosal smears was carried out at the Department of Morbid Anatomy and Histopathology at the University of Health Sciences (UHS), Lahore from April 2011 and December 2012. The study was performed after approval by the Ethical Review Committee of the UHS Lahore. After taking informed consent, 300 subjects were included in the study, majority of them were approached at pan stalls/shops where they came to purchase betel quid. However, some of the samples were also obtained from Mayo Hospital and Punjab Dental Hospital Lahore. Thus, the sampling technique used in this study was a non-probability convenience sampling. The criteria for sample selection included both male and female habitual pan chewers of all ages, who have been chewing pan for at least the past 5 consecutive years. Occasional pan chewers and inadequate smears were excluded from study. Related socio-demographic information (name, age, gender, history of other risky habits, average number of pan consumption in a day and type of pan used, etc) was recorded. In order to make it easy to understand, all subjects were categorized (on the basis of frequency of intake) into light, moderate and heavy pan users. Those who were consuming upto5 pans per day were categorized as 'mild pan chewer'. Similarly, more than 5 but not exceeding 10 per day were graded as 'moderate' whereas those exceeding 10 were kept in a separate category of 'heavy' pan users. After history taking, relevant examination of oral cavity and neck lymph nodes was performed. All subjects were requested to properly rinse their mouth. Oral buccal mucosa was scrapped with the help of a wooden spatula and smeared on to a glass slide. The smears were fixed with ethyl alcohol (70 parts) and ether (30parts) solution for 30 seconds. After air-drying the slides, these were then subjected to staining procedures following the staining protocol of Eosin & Hematoxylin, Giemsa and Papanicolaou's stains. After staining, slides were ready to be viewed under light microscope. All relevant information was transferred to a specially designed proforma. After compilation, data was entered and analyzed using Statistical Package for Social Sciences (SPSS) version 18.0. Frequency and percentage were given for qualitative variables. Means ± SD were given for quantitative variables.

RESULTS

This study included 300 pan chewers around various pan shops located within Lahore were included. Mean age for habitual pan chewing was calculated to be 32.28±0.59 (Range: 17 – 70) years. A large number of them were males (n= 285, 95%) and only 15(5%) were females. The majority (53%) belonged to the lower socio-economic class. The largest percentage of pan chewers happened to be laborers as shown in Figure-1.

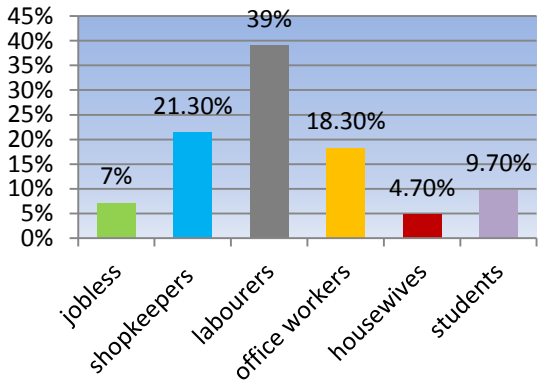


Figure-1 Occupations of the pan chewers

When the oral cavity was thoroughly examined, majority of the subjects (n=148, 49.3%) were found to have discolored teeth. 74 (24.7%) pan chewers complained of hot and cold sensation. Bleeding gums were observed in 71 (23.7%) and painful oral mucosal lesions in 7 (2.3%) individuals. A

large number of habitual pan chewers were also found to be indulged in cigarette smoking (n=103, 34.3%). Alcoholism was observed in 3.3% (n=10) as shown in Figure-2.

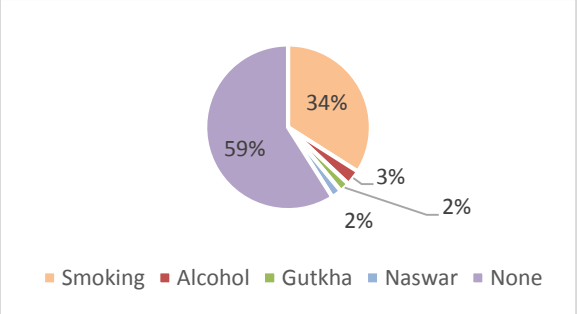


Figure 2. Additional habits among habitual pan chewers

When mean for the total duration of quid chewing was calculated among the study population, it was found to be 11.47±0.39 (Range: 5 – 50) years. The average consumption of betel quid in a day was classified into mild (1 – 5 pans/day), moderate (6 – 10 pans/day) and severe (>10 pans/day). More than half of the study group fell into the mild class of pan users(n=157, 52.3%), the detail is shown in Table-1.

Category	Frequency	Percentage
Mild user (1 – 5 pans/day)	157	52.3%
Moderate user (6 – 10 pans/day)	100	33.3%
Severe user (>10 pans/day)	43	14.4%

Table-1. Pan consumption per day in 300 subjects

In our study, we found that majority of pan users were in the habit of adding tobacco to their pans (n=282, 94%), however there were only few (n=18, 6%) who used to get themselves simple pans without adding tobacco. Nearly half of the study population (n=138, 46%) were in the habit of keeping pans in their left oral vestibule whereas another large proportion (n = 125, 41.7%) used to place pan in their right vestibular area. However, it has been observed that only a few persons were placing it on either (left/right) sides of their oral cavity. When oral cavities of these subjects were thoroughly examined, various oral mucosal lesions were encountered as given in Table-2 & 3.

Oral Mucosal Lesions on naked eye examination	Frequency	Percentage
White lesions	26	8.7%
Red-white lesions	07	2.3%
Fibrotic mucosa	05	1.7%
Red lesions	03	1.0%
Ulcerated growth / mass	03	1.0%

Table 2. Oral mucosal lesions on naked eye examination

Oral Mucosal Lesions on Microscopy / Cytology	Frequency	Percentage
Epithelial dysplasia - Mild - Moderate - Severe	173 65 75 33	57.7 21.7 25 11
Squamous cell carcinoma	03	1.0
Keratosis	163	54.3
Inflammation - Lymphocytes predominant - Lymphocytes and Eosinophils - Mixed (acute and chronic) - Eosinophils - Neutrophils	 224 76 70 56 41 09	 74.7 25.3 23.3 18.7 13.7 3.0
Bacteria - Minimal to moderate load - Heavy load	 146 111 35	 48.7 37 11.7
Candida - Minimal to moderate load - Heavy load	 23 17 06	 7.7 5.7 2.0

Table 3. Oral mucosal lesions on microscopy/cytology

DISCUSSION

The current study discusses some initial cyto-morphological transformations that arise within the oral cavity of chronic pan users. Our study comprised of 300 pan users from different areas within Lahore. The majority of them were males while only few

were females. This prevalence of males in this study was attributed to the fact that the samples taken from various pan shops that are usually seen crowded with males. Women in this part of world, are usually reluctant to visit these pan shops. The reason behind this hesitancy is certainly religious, social and cultural norms. Secondly, males population is more inclined towards habitual pan and tobacco chewing. Several previously published studies have also supported the preponderance of male pan users which is in accordance with our study.[8]

Misra and colleagues reported that their study population mainly consisted of those pan users, who have been daily consuming a minimum of 10 or more than 15 pans, for longer durations of time. They found that chronically pan chewing habits could predispose oral mucosa to early dysplastic changes, which can then act as a precursor for precancerous and frank malignant lesions.[9] Pan war and friends conducted a study with similar findings. They confirmed that oral dysplastic changes are more frequently observed in those individuals who had been practicing tobacco pan chewing continuously for more than 5 years.[10] Rubinstein conducted his study on United States population. He observed that habitual tobacco chewing is becoming prevalent in his study population and is gradually on rise. This continuous practice of tobacco chewing results in oral epithelial dysplasia that later on can take the form of epithelial malignancy.[11] Wen and colleagues showed that habitual chewing of betel quid may cause irritation of the oral mucosa. In addition chronic inflammation, oxidative stress, and cytokine production due to pan chewing may further damage the mucosa. This damaged mucosa can then harbor changes induced by carcinogens produced by long term use of betel quid.[12] Their study also confirmed the role of genes in malignant and premalignant lesions. Carcinogens produced by betel quid components may compromise the genomic stability of tissues, the key for malignant transformation in oral epithelial cells. Another study using Next-Generation sequencing revealed a novel single nucleotide polymorphism (SNP) in multiple cancer-related genes (AR, BRCA1, IL8, and P53). Yadav and his colleagues reported the strong correlation of areca nut derived are coline with single nucleotide polymorphisms in these above-mentioned genes. Similarly, novel deletions in APC, BRMS1, CDK2AP1, CDKN2B, GAS1, IGF1R and RB1 and novel insertions in BRCA2, MSH6, RASSF1, IGF1R, BARD1, and CCND2 were also found associated with areca nut.(13) There are many other studies which also support the notion as well as provide clear evidence for the carcinogenic and pathogenetic role of betel-quid and its components.[14-17]

In our study, the habit of pan chewing was found to be 19 times more prevalent in males individuals as compared to women and the young adults were the commonest age group as depicted by the average age of 32 years. More than half of the pan chewers were from low social background. A few of them gave a history of cigarette smoking, alcohol, and other similar additions. Many of them had discolored teeth which were sensitive to hot and cold and they also had bleeding gums and painful oral lesions despite that majority of them were not concerned with their oral health. They were having pan chewing habits for more than a decade on the average and nearly half of them used to chew 1-5 pans /day. The remaining half had been chewing more than 5 pans/day. Although the calculations of pan chewing/day were based on subject's recall yet can be somewhat arbitrary. Subjects could not mention exact number of pans taken in last 3 days or last 24 hours. So the authors asked them whether they were taking 1-5, 6-10 or more than 10 pans/day and all of the subjects could segregate themselves into one of these categories. That's why we assume it as one of our study limitations and suggest that exact quantification of pan consumption may

require more strenuous efforts in the form of a prospective study like Little et al.[18]

The findings of clinical examination of oral cavity like white lesions, mixed red white, fibrotic, red lesions and ulcerated growth/mass were seen in a few of the subjects whereas cytological examination revealed epithelial dysplasia, keratosis, inflammation, bacterial and candidal loads were observed in 57.7%, 54.3%, 74.7%, 48.7%, and 7.7% subjects respectively. Last but the most important was the incidental diagnosis of 3 cases of oral squamous cell carcinoma in so-called 'healthy' pan chewers. Our findings are consistent with those of previous investigators.[6, 19-23] Nonetheless, these findings are ominous, most of the pan chewers neither took notice of them and nor sought medical advice. This fact is even more worrisome and needs international, national and volunteer efforts by organizations and individuals to embark on effective campaigns against this deadly addition leading to bans and legislation and ultimately reduction in the pan consumption.

CONCLUSION

Poor orodental hygiene, inflammatory conditions, white & red lesions, epithelial dysplasia and malignancy of oral mucosa were alarmingly common in pan chewers from Lahore, Pakistan who belonged to the poor socioeconomic background and do not seek medical advice.

ACKNOWLEDGMENT

Authors are grateful to all the pan shop owners, administration of Mayo Hospital Lahore and University of Health Sciences and Mr. Sameer Anjum, (Laboratory Technician at the Department of Morbid Anatomy and Histopathology), UHS Lahore.

REFERENCES

1. Ho MC. Commentary on Lee et al. (2014): Betel-quid-when East encounters West. Addiction. 2014 Jul;109(7):1205-6.
2. Yap SF, Ho PS, Kuo HC, Yang YH. Comparing factors affecting commencement and cessation of betel quid chewing behavior in Taiwanese adults. BMC Public Health. 2008;8:199.
3. Tsai KY, Su CC, Lin YY, Chung JA, Lian Ie B. Quantification of betel quid chewing and cigarette smoking in oral cancer patients. Community Dent Oral Epidemiol. 2009 Dec;37(6):555-61.
4. Betel-quid and areca-nut chewing and some areca-nut derived nitrosamines. IARC Monogr Eval Carcinog Risks Hum. 2004;85:1-334.
5. Shah SM, Merchant AT, Luby SP, Chotani RA. Addicted schoolchildren: prevalence and characteristics of areca nut chewers among primary school children in Karachi, Pakistan. J Paediatr Child Health. 2002 Oct;38(5):507-10.
6. Mohan BC, Angadi PV. Exfoliative cytological assessment of apparently normal buccal mucosa among quid chewers using argyrophilic nucleolar organizer region counts and Papanicolaou staining. Acta Cytol. 2013;57(2):164-70.
7. Ghani WM, Razak IA, Yang YH, Talib NA, Ikeda N, Axell T, et al. Factors affecting commencement and cessation of betel quid chewing behaviour in Malaysian adults. BMC Public Health. 2011;11:82.
8. Jacob BJ, Straif K, Thomas G, Ramadas K, Mathew B, Zhang ZF, et al. Betel quid without tobacco as a risk factor for oral precancers. Oral Oncol. 2004 Aug;40(7):697-704.
9. Misra V, Singh PA, Lal N, Agarwal P, Singh M. Changing pattern of oral cavity lesions and personal habits over a decade: hospital based record analysis from allahabad. Indian J Community Med. 2009 Oct;34(4):321-5.
10. Panwar SK, Ansari SM, Mulla SK. Oral Precancerous Lesions in Tobacco Users attending Dental Outdoor in Jhalawar District of Rajasthan. National Journal of Community Medicine. 2012;3(3):502.
11. Rubinstein I, Pedersen GW. Bacillus species are present in chewing tobacco sold in the United States and evoke plasma exudation from the oral mucosa. Clin Diagn Lab Immunol. 2002 Sep;9(5):1057-60.

12. Wen CP, Tsai MK, Chung WS, Hsu HL, Chang YC, Chan HT, et al. Cancer risks from betel quid chewing beyond oral cancer: a multiple-site carcinogen when acting with smoking. Cancer Causes Control. 2010 Sep;21(9):1427-35.
13. Yadav DS, Chattopadhyay I, Verma A, Devi TR, Singh LC, Sharma JD, et al. A pilot study evaluating genetic alterations that drive tobacco- and betel quid-associated oral cancer in Northeast India. Tumour Biol. 2014 Jun 19.
14. Chen PH, Lee KW, Hsu CC, Chen JY, Wang YH, Chen KK, et al. Expression of a Splice Variant of CYP26B1 in Betel Quid-Related Oral Cancer. Scientific World Journal. 2014;2014:810561.
15. Wu SY, Lin KC, Chiou JF, Jeng SC, Cheng WH, Chang CI, et al. MicroRNA-17-5p post-transcriptionally regulates p21 expression in irradiated betel quid chewing-related oral squamous cell carcinoma cells. Strahlenther Onkol. 2013 Aug;189(8):675-83.
16. Wang YY, Lin YC, Hung HC, Tien WY, Shieh TY. Polymorphisms in Kallikrein7 and 10 genes and oral cancer risks in Taiwan betel quid chewers and smokers. Oral Dis. 2013 Nov;19(8):824-32.
17. Song H, Wan Y, Xu YY. Betel Quid Chewing Without Tobacco: A Meta-analysis of Carcinogenic and Precarcinogenic Effects. Asia Pac J Public Health. 2013 May 10.
18. Little MA, Pokhrel P, Murphy KL, Kawamoto CT, Suguitan GS, Herzog TA. The reasons for betel-quid chewing scale: assessment of factor structure, reliability, and validity. BMC Oral Health. 2014;14:62.
19. Liao CT, Wallace CG, Lee LY, Hsueh C, Lin CY, Fan KH, et al. Clinical evidence of field cancerization in patients with oral cavity cancer in a betel quid chewing area. Oral Oncol. 2014 Aug;50(8):721-31.
20. Javed F, Yakob M, Ahmed HB, Al-Hezaimi K, Samaranayake LP. Oral Candida carriage among individuals chewing betel-quid with and without tobacco. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013 Oct;116(4):427-32.
21. Reichart PA, Warnakulasuriya S. Oral lichenoid contact lesions induced by areca nut and betel quid chewing: a mini review. J Investig Clin Dent. 2012 Aug;3(3):163-6.
22. Lee CH, Lee KW, Fang FM, Wu DC, Tsai SM, Chen PH, et al. The neoplastic impact of tobacco-free betel-quid on the histological type and the anatomical site of aerodigestive tract cancers. Int J Cancer. 2012 Sep 1;131(5):E733-43.
23. Lee CH, Ko AM, Yen CF, Chu KS, Gao YJ, Warnakulasuriya S, et al. Betel-quid dependence and oral potentially malignant disorders in six Asian countries. Br J Psychiatry. 2012 Nov;201(5):383-91.

Original Article

SERUM PROLACTIN LEVELS IN WOMEN HAVING HIRSUTISM

Muhammad Sohail Aslam,[1] Hamid Javaid Qureshi,[2] Shumaela Kanwal[3] Misbah ul Qamar[4]

ABSTRACT

Objective: To determine the relationship between serum prolactin levels and the severity of hirsutism.

Methods: A sample of sixty female subjects, aged 18-35 years, having hirsutism was selected, while ten normal healthy females were randomly included as controls at IMBB, the University of Lahore in 2014. All subjects underwent an assessment of excess terminal hair growth using the modification of the method originally described by Ferriman and Gallwey (FG). Hirsutism was classified as mild (score 8-15), moderate (score16-25), and severe (score >25). Serum prolactin levels were assayed by ELISA technique. The significance of the difference between the groups was analyzed by independent samples Student's t-test and Pearson's correlation coefficient.

Results: Serum prolactin was significantly (p=0.000) higher in mild hirsute and non significantly(p=0.062) higher in moderate hirsute subjects as compared to the control subjects. The prolactin levels were non significantly correlated to mild hirsutism (r=0.072, p=0.615) and to moderate hirsutism (r=0.076, p=0.846).

Conclusion: Serum prolactin is raised in hirsute women, however, the relationship between serum prolactin and severity of hirsutism is not statistically significant.

Key Words: Hirsutism, Androgens, Prolactin.

INTRODUCTION

Hirsutism refers to the presence of excessive coarse hair in androgen-dependent areas of the female body. Although hirsutism is commonly considered as an aesthetic problem, there is a high prevalence of androgen excess disorders among hirsute women. Although not all women suffering from an androgen-excess disorder have hirsutism, however depending on age, race, and ethnicity, 80–90% of hirsute patients will have a demonstrable androgen-excess disorder.[1,2]

Many scoring methods based on visual assessment of hair type and growth have been proposed. The modified Ferriman Gallwey score (mFG) proposed by Hatch et al. has now become the gold standard for the evaluation of hirsutism.

This method scores 9 of the 11 body areas (upper lip, chin, chest, upper and lower back, upper and lower abdomen, arm, forearm, thigh and lower leg) originally proposed by Ferriman and Gallwey (1961), excluding the lower legs and forearms, which are the areas sensitive to very low androgen concentrations even in healthy women.[3]

The main causes of hirsutism include excessive production of androgens by female adrenal glands and ovaries. Uncommonly, increased prolactin levels can also result in hirsutism. This study was carried out to investigate the relationship of prolactin with hirsutism in the local female population of Lahore.

METHODS

This case-control study was conducted at the Institute of Molecular Biology & Biotechnology, University of Lahore, on 60 hirsute female subjects and 10 normal healthy females aged 18-35 years.

[1] Associate Professor Physiology AMDC, Lahore.
[2] Professor Physiology AMDC, Lahore.
[3] Associate Professor Physiology AMDC, Lahore.
[4] Assistant Professor Physiology AMDC, Lahore.

Inclusion criteria comprised patients of hirsutism with a modified Ferriman-Gallwey (mF-G) score of eight or more, patients presenting with oligo/amenorrhea, ovulatory dysfunction, excess hair growth, virilization, alopecia, or acne.

Exclusion criteria included pregnant or lactating women, those who received oral contraceptive pills or/and other anti-androgen drugs in the previous three months, those who received drugs known to cause hirsutism or interfere with the hormonal studies. Patients with a modified Ferriman-Gallwey (mF-G) score of less than 8 were also excluded.

The study was approved by the Ethical Review Committee of the Institute of Molecular Biology & Biotechnology, University of Lahore.

All the subjects completed a standardized history and clinical proforma, including questions about age, family history of hirsutism, onset and duration of the disorder, marital status, menstrual cycle length and regularity, other illnesses, and medications.

The subjects also underwent an assessment of excess terminal hair growth using the previously described modification of the method originally described by Ferriman-Gallwey (i.e. mF-G), scoring the presence of terminal hairs over nine body areas (upper lip, chin, chest, upper and lower abdomen, thighs, upper and lower back, and upper arms). Hirsutism was classified as mild (score 8-15), moderate (score16-25), and severe (score >25).

The blood samples for prolactin assay were obtained, after informed consent, by standard venepuncture technique; Three to four ml of venous blood was drawn from the cubital vein. The blood samples were centrifuged at 4,000 rpm and the serum samples were aliquoted and stored at -20^{o}C until used. The hormone assay was done by ELISA technique.

The demographic variables were presented as simple descriptive statistics calculating mean and SD of numerical data like age, duration of the disorder, and modified Ferriman-Gallwey (mFG) scores of hirsutism.

The significance of the difference between the groups was analyzed by independent samples Student's t-test and Pearson's correlation coefficient was determined to find out correlation. A p-value < 0.05 was considered statistically significant. All statistical analyses were carried out with SPSS version 17.

RESULTS

Sixty hirsute female subjects enrolled in this study, had their ages ranged from 18-35 years with a mean± SD age of 24.58± 0.57 years. The control group had a mean± SD age of 25.6 ± 1.76 years. The statistical difference regarding the parameter of age between the two groups was non-significant ($p = 0.13$). About 72% of the subjects had the hirsute symptoms for shorter duration i-e up to maximum of 5 years and less. The rest had the disorder for more than 5 up to 14 years. The duration of the disease ranged from 1-14 years. A family history of hirsutism was positive in 12 (20%) patients.There was history of regular menstrual cycle in 47 patients (78.33%) and irregular menstruation in 13 patients (21.66%).Table 1.

Table 1. General features of the hirsute subjects

Parameter		n	%
Duration in years	1-5	43	72
	6-14	17	28
Menstrual cycle	Regular	47	78
	Irregular	13	22
Family history	Yes	12	48
	No	20	80

Serum prolactin levels were significantly ($p< 0.05$) higher in hirsute women as compared to that in controls. The level of the hormone was 58% ($p=0.000$) higher in mild hirsute and 44% ($p=0.062$) higher in moderate hirsute subjects as compared to the control subjects. Table 2 & Figure 1.

Table2. Serum prolactin levels in the control group and hirsute group with mild and moderate hirsutism.

Group		No	Mean± SDSerum prolactin (mIU/L)	% Change to controls
Control		10	166.09±12.37	
Hirsute	Mild	51	395.68±26.91	58*
	Moderate	9	301.06±61.66	44

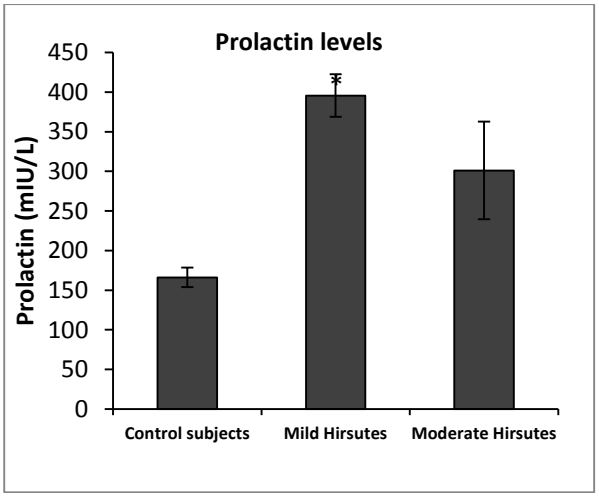


Fig.1. Serum prolactin levels in control subjects and hirsute subjects with mild and moderate hirsutism.

Serum prolactin levels were positively related to mild hirsutism (r=0.072, p=0.615) and to moderate hirsutism (r=0.072, p=0.846). However, the correlations were not statistically significant. Table 3.

Table 3. Correlation of serum prolactin levels with mild and moderate hirsutism

Prolactin	Correlation Coefficient (r)	p-Value
Mild Hirsutism	0.072	0.615
Moderate Hirsutism	0.076	0.846

(*p≤ 0.05. Statistically Significant)

DISCUSSION

Perception of hirsutism is highly subjective, and hirsute women present with a wide variation in severity. Hirsutism is no longer a cosmetically disfiguring condition, but it can serve as a pointer to underlying hormonal and other systemic conditions. The rational differential diagnosis of this condition is therefore of much importance. Increased prolactin levels are amongst the rarer causes of hirsutism.

The direct action of prolactin on adrenal steroidogenesis has been reported.[4] Prolactin has receptors in all three layers of the adrenal cortex. Stimulation by prolactin is reported to increase adrenal androgens, dehydroepiandrosterone and dihydro-epitestosterone sulfate as well as cortisol and aldosterone.[5]

In the present study, serum prolactin levels were found higher in the hirsute subjects. The comparison of mean values of mFG scores in patients with mild and moderate hirsutism and the control groups revealed significant differences. These results are comparable with the results of a study about the levels of prolactin with hirsutism in Bangladesh which showed increased prolactin levels in hirsute subjects.[6]

Similarly, another study in India found increased prolactin levels in hirsute women.[7] However, in a study in 1007 women with polycystic ovary syndrome, prolactin levels were found lower in patients as compared to controls.[8]

In our study, the prolactin levels were related to mild and moderate hirsutism. However, the differences among the groups were not statistically significant. Similar results were observed in a study carried out by Hertweck[9] et al in which no evidence of a statistical relationship was found between hirsutism score and prolactin. In another study by Zadehmodarres et al, statistical differences were found not significant regarding hirsutism and prolactin.[10]

Being a rarer cause and also because of a dearth of work, hyperprolactinemia needs to be probed further in the causation of hirsutism, especially in our local population.

CONCLUSION

Serum prolactin is raised in hirsute women, however, its relationship with the severity of hirsutism is not statistically significant.

REFERENCES

1. Azziz R, Sanchez LA, Knochenhauer ES, Moran C, Lazenby J, Stephens KC, Taylor K, Boots LR. Androgen excess in women: experience with over 1000 consecutive patients. The Journal of Clinical Endocrinology & Metabolism. 2004 Feb 1;89(2):453-62.
2. Carmina E, Rosato F, Janni A, Rizzo M, Longo RA. Relative prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism. The Journal of Clinical Endocrinology & Metabolism. 2006 Jan 1;91(1):2-6.
3. BO BS, Woods K. Visually scoring hirsutism. Hum Repro Update. 2010;16(1):54-64.
4. Freeman ME, Kanyicska B, Lerant A, Nagy G. Prolactin: structure, function, and regulation of secretion. Physiological reviews. 2000 Jan 10;80(4):1523-631.
5. Moria Y, Kortbawi R, Nadine EA, Arafah BM. Increased androgen secretion in patients with prolactinomas: the impact of altered HPA function. Pituitary. 2019 Apr 15;22(2):170-8.
6. Islam S, Pathan F, Ahmed T. Clinical and Biochemical Characteristics of Polycystic Ovarian Syndrome among Women in Bangladesh. Mymensingh medical journal: MMJ. 2015 Apr;24(2):310-8.
7. Tirgar-Tabari S, Sharbatdaran M, Manafi-Afkham S, Montazeri M. Hyperprolactinemia and hirsutism in patients without polycystic ovary syndrome. International journal of trichology. 2016 Jul;8(3):130.
8. Glintborg D, Altinok M, Mumm H, Buch K, Ravn P, Andersen M. Prolactin is associated with metabolic risk and cortisol in 1007 women with polycystic ovary syndrome. Human Reproduction. 2014 Jun 4;29(8):1773-9.
9. Hertweck SP, Yoost JL, McClure ME, Siow Y, Brock GN, Wintergerst KA, Fallat ME. Ferriman-Gallwey scores, serum androgen and mullerian inhibiting substance levels in hirstute adolescent girls. Journal of pediatric and adolescent gynecology. 2012 Oct 1;25(5):300-4.
10. Zadehmodarres S, Heidar Z, Razzaghi Z, Ebrahimi L, Soltanzadeh K, Abed F. Anti-mullerian hormon level and polycystic ovarian syndrome diagnosis. Iranian journal of reproductive medicine. 2015 Apr;13(4):227.

Original Article

GENDER DIFFERENCE IN PATIENT'S SATISFACTION IN TERTIARY CARE HOSPITALS OF LAHORE.

Tehseen Bokhari[1], Iram Manzoor[2], Aiman Dawood[3], Ujala Arshad[4], Zoha Mahmood[4]
Jamaal Hassan Ali[4], Abida Hassan[5]

ABSTRACT:
Objectives: Quality of health care services is a global affair. Effective quality health services are measured for quality management in hospitals. Patient satisfaction is a major indicator to measure the quality management of hospitals. The main objective of this study is to assess gender difference in setisfection level of patients coming to tertiary health care facilities in Lahore
Methods: An analytical cross-sectional study was conducted from January to August 2018 in two tertiary care hospitals of Lahore including Akhtar Saeed Trust Teaching Hospital and Farooq Hospital, Westwood branch. A sample of 200 patients was collected, using Non-Probability, consecutive technique. Data was collected by using a self-structured questionnaire with multiple variables related to services, an attitude of health care providers and the environment of hospitals. Data was entered and analyzed using SPSS 22. The chi-square test was applied and the p-value was fixed at ≤0.05 as significant.
Results: Out of 200 participants, 109 (86.5%) were males and 91 (45.5%) were females. The overall satisfaction rate of patients was reported at 93% with no significant difference in the satisfaction level of both genders. Females were much more satisfied with hospital services. Regarding waiting time 91.2% of the females were satisfied (p = 0.007), comfortable waiting area was reported by 93.4% of the females (p=0.001). Females were more satisfied with examination in clean environment (p= 0.004) and Lab services (p= 0.002). Regarding satisfaction parameters related to health care providers, females were more satisfied with provision of privacy (p= 0.002), treatment with respect and dignity (p=0.038), correct diagnosis (p=0.042), adequate time (p= 0.03), careful attitude (p= 0.025) and adequate knowledge (p=0.031).
Conclusion: Females show a higher satisfaction level as compared to males regarding services offered to them in these tertiary care hospitals of Lahore.

Key Words: Patient satisfaction, Gender Differences, Tertiary Healthcare Hospital.

INTRODUCTION:

Quality of healthcare is a global affair and patient satisfaction is the key element to assess the quality of healthcare services.[1,2] Patient satisfaction is measured in terms of expense, approachability of health services and patient fast recovery.[3] Patient satisfaction is also based upon the expectations of the patient and their actual experience of receiving healthcare services.[4,5] Provision of patient centered-care is essential and is directly related to satisfaction.[6]

Multiple standardized questionnaires have been widely used to measure the satisfaction level of patients in various parts of the world.[7] Patient satisfaction is influenced by some common determinants and predictors.[5,7] Demographic factors like age, gender, education level, socio-economic status and functional status of the patient greatly affect their satisfaction levels regarding health care service provision.[5,8,9] According to a study, in the USA; the male gender, age greater than 50 years, short hospital stay and primary level of education had shown more level of satisfaction.[10] While some studies demonstrated the opposite result where patients were satisfied

[1] Student AMDC, Lahore.
[2] Professor Community Medicine, AMDC, Lahore.
[3] Demonstrator Community Medicine, AMDC.
[4] Student AMDC, Lahore.
[5] Assistant Professor Community Medicine, AMDC.

with longer hospital stay.[11] Regarding gender, male patients were more satisfied in Israel while female patients demonstrated higher satisfaction rates in Saudi Arabia.[8] Various other factors affected the level of satisfaction inversely, including long waiting times and heavy registration of patients.[12]

According to a study conducted in Malaysia gender, income level and purpose of visit to a hospital play a key role inttaining high satisfaction levels among patients.[13] In Pakistan, previously many studies had considered the patient satisfaction level as a measuring tool for the health care system. According to research conducted in Peshawar, in private sector hospitals mean patient satisfaction score was 121.94 ± 20.84 as compared to public sector hospitals, which was lower in value by 104.97 ±18.51 ($p < 0.001$).[14] A critical review comprising of many studies revealed that elder age, male gender, higher socioeconomic status, and education had positive affect on patient satisfaction.[15]

This study was conducted to assess the patient satisfaction level by considering the gender difference as a predicting factor in patient satisfaction levels.

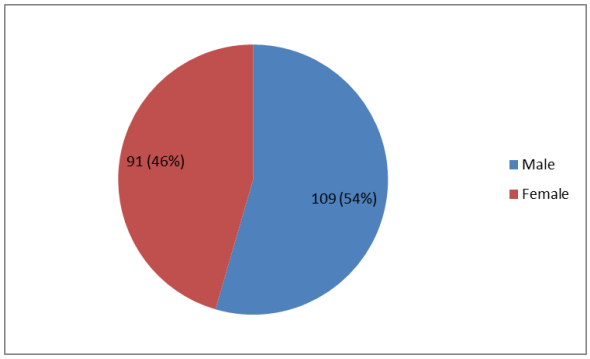
METHODS:

This was an analytical cross-sectional study conducted in two tertiary care hospitals situated in Lahore between January to August 2018. Two hundred patients were recruited from Akhtar Saeed Trust Teaching Hospital and Farooq Hospital, Westwood branch. Both male and female patients above 18 years of age were recruited by using nonprobability consecutive sampling after taking informed consent. Data was collected by using a structured questionnaire with multiple variables related to satisfaction about health care providers, services and hospital environment. Data were analyzed using SPSS version 22 and the data was presented in the form of Likert scale, pie chart and frequency tables. Chi-square test of significance was applied to assess the gender difference in satisfaction level of patients keeping p-value of ≤0.05 as significant.

RESULTS:

This study consisted of a sample of about 200 patients, out of which 54.5% were males and 45.5% were females. (**Figure 1)**

Figure 1: Distribution of gender among respondents



To assess the patient's satisfaction level, multiple variables were included in different parameters related to the hospital, health care provider, and patient. Regarding parameters of hospital, higher satisfaction levels were observed with ease to make an appointment (86.5%), convenience in approaching hospital (74.5%), reasonable waiting time (83.5%), comfortable waiting room (84.5%), examination in a clean and safe environment (87%) and lab and radiology services (86.5%). Satisfaction with affordable hospital services was slightly lower with 59% satisfaction level.

Satisfaction with parameters related to the doctor revealed that 91.5% of respondents said that they were involved in decisions about their treatment. One hundred and eighty-four (92%) of the respondents were satisfied with the communication skills of the doctor. Satisfaction with the provision of privacy was shown by 86.5% of respondents and 91% respondents said that they were treated with dignity. The provision of complete information was shown by 94% respondents and 97% respondents agreed that their personal information was kept confidential. Satisfaction with effective treatment was shown by 97.5%. Lower satisfaction levels were reported with correct diagnosis (61.5%), adequate time provision by doctor (73.5%), attitude of doctor (77.5%)

and adequate knowledge (74%). One hundred and thirty-five respondents (67.5%) felt that doctor on duty used medical terminology after explaining the term and 85% were satisfied with the caring attitude of the doctor.

The satisfaction level of patients revealed that 93.5% of respondents had confidence and trust in their doctor providing treatment. Only 25% of the respondents felt ignored by the doctor on duty. Expensive medical treatment was pointed out by 55% of the respondents, who said that they sometimes go without medical care because it is expensive. Overall 93% of the respondents were satisfied with the doctors and medical services and among them, 89% would recommend these hospitals to their relatives**. (Table 1)**

Table 1: Variables to assess the satisfaction of respondents (n=200)

Parameter to measure satisfaction	Frequency (n) Yes	Percentage (%)
Related to hospital:		
Easiness to make an appointment	173	86.5%
Convenience in approaching the hospital	149	74.5%
Reasonable waiting time	167	83.5%
Comfortable waiting room/OPD	169	84.5%
Examination in a clean and safe environment	174	87%
Affordable hospital services	118	59%
Satisfaction with radiology and lab services	173	86.5%
Related to Health care provider/ Doctor on duty		
Involvement in decisions making about care	183	91.5%
Doctor's communication skills	184	92%
Provision of privacy	173	86.5%
Treatment with dignity	182	91%
Provision of adequate information	188	94%
Maintenance of confidentiality	194	97%
Provision of effective treatment	195	97.5%
Correctness of the diagnosis	123	61.5%
Provision of doctor's time	147	73.5%
Attitude of the doctor towards the respondent	155	77.5%
Careful attitude while examination	170	85%
Use of Medical terminology	135	67.5%
Adequate knowledge	148	74%
Related to patient		
Confidence and trust in the doctor	187	93.5%
Feeling of being ignored	50	25%
Expensive treatment	110	55%
Recommendation of hospitals to others	178	89%
Overall satisfaction level	186	93%

When the gender of the respondents was taken into consideration the results of this study showed that female patients were more satisfied with a percentage of 94.5% as compared to 91.7% males. Gender differences were observed in reasonable waiting time (p= 0.007), comfortable waiting room (p= 0.001) examination in a clean and safe environment (p=0.004), radiology and lab services (p= 0.002) where females showed greater satisfaction with services. Females showed higher satisfaction levels with the provision of privacy (p=0.002), treatment with dignity and respect (p=0.038), correct diagnosis (p=0.042), adequate time provision by doctor (p=0.003), careful attitude of doctor (p=0.025) and adequate knowledge of

doctor (p=0.031). No gender difference was observed in overall satisfaction level of patients with p-value of 0.446. **(Table 2)**

Table 2: Association of gender with the satisfaction level

Satisfaction with parameters related to hospital				
Variables to assess satisfaction	**Gender**	**Yes**	**No**	**p value**
Easiness to make an appointment	Male	96(88.1%)	13 (11.9%)	0.476
	Female	77(84.6%)	14(15.4%)	
Convenience in approaching the hospital	Male	80(73.4%)	29(26.6%)	0.695
	Female	69(75.8%)	22(24.2%)	
Reasonable waiting time	Male	84(77.1%)	25(22.9%)	**0.007***
	Female	83(91.2%)	8(8.8%)	
Comfortable waiting room/OPD	Male	84(77.1%)	25(22.9%)	**0.001***
	Female	85(93.4%)	6(6.6%)	
Examination in a clean and safe environment	Male	88(80.7%)	21(19.3%)	**0.004***
	Female	86(94.5%)	5(5.5%)	
Affordable hospital services	Male	67(61.5%)	42(38.5%)	0.437
	Female	51(56.0%)	40(44.0%)	
Satisfaction with radiology and lab services	Male	87(79.8%)	22(20.2%)	**0.002***
	Female	86(94.5%)	5(5.5%)	
Satisfaction with parameters related to doctor				
Involvement in decision making about care	Male	98(89.9%)	11(10.1%)	0.377
	Female	85(93.4%)	6(6.6%)	
Satisfaction with doctor's communication skills	Male	98(89.9%)	11(10.1%)	0.233
	Female	86(94.5%)	5(5.5%)	
Provision of privacy	Male	87(79.8%)	22(20.2%)	**0.002***
	Female	86(94.5%)	5(5.5%)	
Treatment with dignity	Male	95(87.2%)	14(12.8%)	**0.038***
	Female	87(95.6%)	4(4.4%)	
Provision of adequate information	Male	101(92.7%)	8(7.3%)	0.383
	Female	87(95.6%)	4(4.4%)	
Maintenance of confidentiality	Male	104(95.4%)	5(4.6%)	0.150
	Female	90(98.9%)	1(1.1%)	
Provision of effective treatment	Male	105(96.3%)	4(3.7%)	0.246
	Female	90(98.9%)	1(1.1%)	
Correctness of the diagnosis	Male	74(67.9%)	35(32.1%)	**0.042***
	Female	49(53.8%)	42(46.2%)	
Provision of doctor's time	Males	71(65.1%)	38(34.9%)	**0.003***
	Female	76(83.5%)	15(16.5%)	
Attitude of the doctor towards respondent	Male	79(72.5%)	30(27.5%)	0.063
	Female	76(83.5%)	15(16.5%)	
Careful attitude of the doctor	Male	87(79.8%)	22(20.2%)	**0.025***
	Female	83(91.2%)	8(8.8%)	
Use of medical terms	Male	69(63.3%)	40(36.7%)	0.165
	Female	66(72.5%)	25(27.5%)	
knowledge of doctor	Male	74(67.9%)	35(32.1%)	**0.031***
	Female	74(81.3%)	17(18.7%)	
Satisfaction with parameters related to patient				
Confidence and trust in the doctor providing treatment	Male	97(89.0%)	12(11.0%)	**0.005***
	Female	90(98.9%)	1(1.1%)	
Feeling of being ignored	Male	32(29.4%)	77(70.6%)	0.119
	Female	18(19.8%)	73(80.2%)	
Expensive treatment	Male	59(54.1%)	50(45.9%)	0.786
	Female	51(56.0%)	40(44.0%)	
Recommendation of hospital services to others	Male	94(86.2%)	15(13.8%)	0.172
	Female	84(92.3%)	7(7.7%)	
Overall satisfaction	Male	100(91.7%)	9(8.3%)	0.446
	Female	86(94.5%)	5(5.5%)	

When the level of satisfaction was assessed with the application of Likert scale it was observed that 8% of the participants rated overall hospital as excellent, 27.5% as very good and 48% as good. **(Figure 2)**

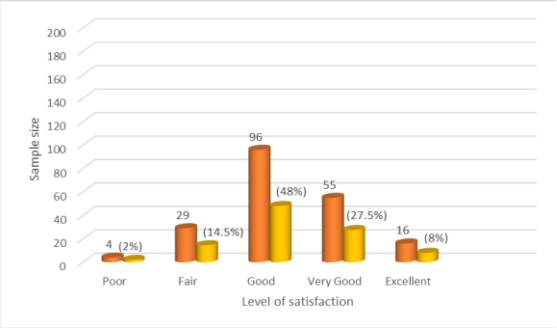


Figure 2: Level of satisfaction with the provision of services

DISCUSSION:

This study was conducted to determine the level of satisfaction of patients attending tertiary care hospitals in Lahore. The results showed that overall 93% of the patients were satisfied, which is similar to another study conducted in India in which 89.1% of patients were generally satisfied. [1] The overall satisfaction level didn't show any significant gender difference.

Overall 86.5% respondents were satisfied with easiness to make an appointment and no gender difference was observed in satisfaction levels. This result is similar to a study conducted in Malaysia, which showed that 79.4% of the respondents thought that it was easy to make an appointment to the hospital.[16] The results of this study revealed that 74.5% of the respondents agreed that it was convenient to approach the hospital with no gender difference. A study conducted in India showed that 84% of the participants had a problem accessing the hospital due to either an ill-maintained road or long waiting time at the bus stop.[1] Results revealed that 83.5% of the patients considered the waiting time to be reasonable. Females were more satisfied with waiting time in comparison to males (p=0.007). This finding is in line with a study conducted in the emergency department of a tertiary care hospital, Bangladesh which showed that the majority of the patients had to wait for five minutes before being examined by the doctor which increase their satisfaction with provision of services.[17] In this study 93.5% female patients were contended with the environment of the waiting room as compared to 77.1% male respondents with a significant p-value of 0.001. Studies suggest that patients identified adequate seating, non-overcrowding, and privacy for conversations as important factors for satisfaction with provision of services of health settings.[18]Approximately 87% of the respondents agreed that they were examined in a clean and safe environment with higher level of satisfaction in the female gender. Studies show that proper housekeeping of the hospitals is important for keeping the patients safe and preventing spread of infections and patients feel more comfortable in clean hospital environment.[19]

In this study 41% respondents affirmed that they had to pay more for their medical care than they could afford. Worldwide it is observed that some patients report non-adherence to therapy as a result of higher out-of-pocket costs.[20, 21]

Informed consent and shared decision making leads to the patient's understanding of their ailments in a better way and openly discussing their treatment plans. [22] In this study, 91.5% of respondents were involved in making decisions about their treatment. An informed consent taken from the patient, using any format, reduces anxiety and increases comprehension of the patient.[23] Assessing patient's understanding after informed consent will allow the clinicians to better manage expectations and improve the outcome and improves patient satisfaction.[24] In this study 92% respondents said that they were satisfied with the communication skills of the doctor on duty and there was no gender difference in satisfaction level observed. More female respondents (94.5%) as compared to male respondents (89.9%) were satisfied at a p-value of 0.233 which was insignificant. Good communication

skills are essential for a doctor which greatly affects satisfaction level of patients regarding doctor's attitude.[25]

The fulfillment of privacy leads to protection, improved communication, and dignity of patients. Better privacy can be ensured by lowering voice or by avoiding discussion of patient's treatment options in the ward where they could be overheard. Some studies have emphasized the importance of staff education in improving patient privacy and satisfaction.[26,27] In this study 86.5% of respondents revealed that they were provided enough privacy including. Females were more satisfied with provision of privacy during examination (p = 0.002) Dignity and privacy are interrelated and lack of one leads to loss of the other.[28] In this study of 200 respondents, 91% of them identified that they were treated with dignity at all times with higher satisfaction level in females with p-value of 0.038. These findings are in contrast to a study that was conducted on female patients showing violation of their dignity in India.[29] Other studies also confirmed that intrapersonal values and attitudes had a central role in preserving or threatening the patients' dignity.[30]

Study findings showed that 94% of respondents agreed that the information they received helped them understand their disease. A study done to compare the communication skills of junior and senior residents suggests that senior residents have an easier time having unpleasant and tough conversations with patients as compared to junior residents.[31] Literature suggests that overcrowding can cause a breach in confidentiality of patient's information with total 75% of breaches occurring during patient handover, examining and performing procedures at inappropriate places and giving patient's credentials to computer personnel at 25% each.[32] In our study 97% respondents agreed that their personal information was kept confidential.

In this study, about 61.5% of respondents did not question the correctness of the diagnosis made by the doctor including 67.9% males and 53.8% females. These results show clear female predominance at a significant p-value of 0.042. Decisions made collectively by the doctor and patient, increase the trust of the patient in the medical care provider.[33]

In this study 83.5% of the female patients were satisfied with a highly significant p-value of 0.003 with the amount of time the doctor spent with them. Research shows that the accuracy of treatment provided by the doctor has a powerful effect on the patients' satisfaction than the actual amount of time and those who are given more time by the doctor are less satisfied showing a negative correlation between time given by the doctor and patient satisfaction.[34]

In this study, 77.5% of respondents were satisfied with the attitude of the doctor with higher levels of female satisfaction. In a study conducted by the Department of Forensic Medicine and Toxicology Tehran, out of the 56 cases, the frequency of malpractice was observed in 48.2 % of the female patients.[35,36] In this study 74% of the respondents agreed that the medical staff providing them treatment was knowledgeable. Worldwide it is accepted that greater knowledgeability leads to better adherence of code of ethics by the doctor which leads to lower rates of malpractice.[37, 38]

Of the total sample, 93.5% of respondents showed confidence and trust in the doctor providing treatment with a higher female satisfaction level. Trust is empirical as it ensures patients' compliance with the instructions given to them. Patients are more confident in the doctors who pay attention to their complaints and needs.[39] In our study 25% of respondents said that the research shows that when the doctors take a dominant role and do one-sided interactions, patients, as well as their families, don't get a chance to clear their queries and feel ignored by their medical care provider.[40] In this study 93% respondents were overall satisfied among whom 89% would recommend the services of these hospitals to their relatives. Many studies revealed that a satisfied patient

refers to other relatives to the facility where he was provided care which overall increases utilization rates and increases the quality of services.[32]

CONCLUSION:

It is concluded that there are multiple factors that affect patient satisfaction levels including factors related to the hospital, services, health care provider and patient himself. Generally, females were found much more satisfied as compared to males with these parameters.

REFERENCES:

1. Qadri SS, Pathak R, Singh M, Ahluwalia SK, Saini S, Garg PK. An assessment of patients' satisfaction with services obtained from a tertiary care hospital in rural Haryana. International Journal of Collaborative Research on Internal Medicine & Public Health. 2012 Aug 1;4(8):1524.
2. Beşciu CD. Patient Satisfaction in the Hospital's Emergency Units in Bucharest. Procedia Economics and Finance. 2015 Jan 1;32:870-7.
3. Faezipour M, Ferreira S. A system dynamics perspective of patient satisfaction in healthcare. Procedia Computer Science. 2013 Jan 1;16:148-56.
4. Shirley E, Josephson G, Sanders J. Fundamentals of patient satisfaction measurement. Physician leadership journal. 2016;3(1):12.
5. Ahmad I, Nawaz A, Khan S, Khan H, Rashid MA, Khan MH. Predictors of patient satisfaction. Gomal Journal of Medical Sciences. 2011;9(2).
6. Naidu A. Factors affecting patient satisfaction and healthcare quality. International journal of health care quality assurance. 2009 Jun 12;22(4):366-81.
7. Al-Abri R, Al-Balushi A. Patient satisfaction survey as a tool towards quality improvement. Oman medical journal. 2014 Jan;29(1):3.
8. Dayasiri MB, Lekamge EL. Predictors of patient satisfaction with quality of health care in Asian hospitals. Australasian Medical Journal (Online). 2010 Sep 18;3(11):739.
9. Alrubaiee L, Alkaa'ida F. The mediating effect of patient satisfaction in the patients' perceptions of healthcare quality-patient trust relationship. International Journal of Marketing Studies. 2011 Feb 1;3(1):103.
10. Otani K, Herrmann PA, Kurz RS. Improving patient satisfaction in hospital care settings. Health Services Management Research. 2011 Nov;24(4):163-9.
11. Quintana JM, González N, Bilbao A, Aizpuru F, Escobar A, Esteban C, San-Sebastián JA, de-la-Sierra E, Thompson A. Predictors of patient satisfaction with hospital health care. BMC health services research. 2006 Dec;6(1):102.
12. Arshad AS, Shamila H, Jabeen R, Fazli A. Measuring patient satisfaction: A Cross Sectional study to improve quality of care at a tertiary care hospital. Health line. 2012 Mar;3(1):43-6.
13. Ganasegeran K, Perianayagam W, Abdul Manaf R, Jadoo A, Ahmed S, Al-Dubai SA. Patient satisfaction in Malaysia's busiest outpatient medical care. The Scientific World Journal. 2015;1-6.
14. Khattak A, Alvi MI, Yousaf MA, Shah SZ, Turial D, Akhter S. Patient satisfaction–a comparison between public & private hospitals of Peshawar. International Journal of Collaborative Research on Internal Medicine & Public Health. 2012;4(5):713-22.
15. Naseer M, Zahidie A, Shaikh BT. Determinants of Patient's satisfaction with health care system in Pakistan: a critical review. Pakistan Journal of Public Health. 2012;2(2):52.
16. Ghani A, MH MZ, Cheah CW. Satisfaction of Patient in Undergraduate Periodontal Clinic at University of Malaya. Annals of Dentistry University of Malaya. 2015 Dec 31;22(2):31-7.
17. Akhtar K, Rashid MM, Akhtar K, Siddika A, Siddika SS. Status and Patients Satisfaction Attended at Emergency Department of a Tertiary Level Hospital in Dhaka City. Journal of Current and Advance Medical Research. 2019 Mar 27;6(1):53-8.
18. Hallock JL, Rios R, Handa VL. Patient satisfaction and informed consent for surgery. American journal of obstetrics and gynecology. 2017 Aug 1;217(2):181-e1.

19. Han JH, Sullivan N, Leas BF, Pegues DA, Kaczmarek JL, Umscheid CA. Cleaning hospital room surfaces to prevent health care–associated infections: a technical brief. Annals of internal medicine. 2015 Oct 20;163(8):598-607.
20. Neugut AI, Subar M, Wilde ET, Stratton S, Brouse CH, Hillyer GC, Grann VR, Hershman DL. Association between prescription co-payment amount and compliance with adjuvant hormonal therapy in women with early-stage breast cancer. Journal of Clinical Oncology. 2011 Jun 20;29(18):2534.
21. Streeter SB, Schwartzberg L, Husain N, Johnsrud M. Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. Journal of oncology practice. 2011 May;7(3S):46s-51s.
22. King J, Moulton B. Group Health's participation in a shared decision-making demonstration yielded lessons, such as role of culture change. Health Affairs. 2013 Feb 1;32(2):294-302.
23. Goldberger JJ, Kruse J, Kadish AH, Passman R, Bergner DW. Effect of informed consent format on patient anxiety, knowledge, and satisfaction. American heart journal. 2011 Oct 1;162(4):780-5.
24. Hall DE, Prochazka AV, Fink AS. Informed consent for clinical treatment. Cmaj. 2012 Mar 20;184(5):533-40.
25. Ranjan P, Kumari A, Chakrawarty A. How can doctors improve their communication skills?. Journal of clinical and diagnostic research: JCDR. 2015 Mar;9(3):JE01.
26. Lin YK, Lin CJ. Factors predicting patients' perception of privacy and satisfaction for emergency care. Emergency Medicine Journal. 2011 Jul 1;28(7):604-8.
27. Nayeri ND, Aghajani M. Patients' privacy and satisfaction in the emergency department: a descriptive analytical study. Nursing ethics. 2010 Mar;17(2):167-77.
28. Baillie L. Patient dignity in an acute hospital setting: a case study. International journal of nursing studies. 2009 Jan 1;46(1):23-37.
29. Söderberg S, Olsson M, Skär L. A hidden kind of suffering: female patient's complaints to Patient's Advisory Committee. Scandinavian Journal of Caring Sciences. 2012 Mar;26(1):144-50.
30. Bagheri H, Yaghmaei F, Ashktorab T, Zayeri F. Patient dignity and its related factors in heart failure patients. Nursing ethics. 2012 May;19(3):316-27.
31. Falcone JL, Claxton RN, Marshall GT. Communication skills training in surgical residency: a needs assessment and metacognition analysis of a difficult conversation objective structured clinical examination. Journal of surgical education. 2014 May 1;71(3):309-15.
32. Calleja P, Forrest L. Improving patient privacy and confidentiality in one regional emergency department–a quality project. Australasian Emergency Nursing Journal. 2011 Nov 1;14(4):251-6.
33. Peek ME, Gorawara-Bhat R, Quinn MT, Odoms-Young A, Wilson SC, Chin MH. Patient trust in physicians and shared decision-making among African-Americans with diabetes. Health communication. 2013 Aug 1;28(6):616-23.
34. Xie Z, Or C. Associations between waiting times, service times, and patient satisfaction in an endocrinology outpatient department: A time study and questionnaire survey. INQUIRY: The Journal of Health Care Organization, Provision, and Financing. 2017 Nov 21;54:0046958017739527.
35. Kazemi S, Mostafazadeh B, Heshmati S, Emamhadi MA. Medical Malpractice in Cardiovascular Surgery; Cases Referred to Tehran Forensic Medicine Organization during 2011-13. International Journal of Medical Toxicology and Forensic Medicine. 2015 Jan 1;5(4 (Autumn)):207-13.
36. Fenton JJ, Franks P, Feldman MD, Jerant A, Henry SG, Paterniti DA, Kravitz RL. Impact of patient requests on provider-perceived visit difficulty in primary care. Journal of general internal medicine. 2015 Feb 1;30(2):214-20.
37. Tiruneh MA, Ayele BT. Practice of code of ethics and associated factors among medical doctors in Addis Ababa, Ethiopia. PloS one. 2018 Aug 8;13(8):e0201020.
38. Wamisho BL, Abeje M, Feleke Y, Hiruy A, Getachew Y. Analysis of medical malpractice clams and measures proposed by the health professionals ethics federal committee of Ethiopia: review of the three years proceedings. Ethiop Med J. 2015 Jan;53(Suppl 1):1-6.

39. Croker JE, Swancutt DR, Roberts MJ, Abel GA, Roland M, Campbell JL. Factors affecting patients' trust and confidence in GPs: evidence from the English national GP patient survey. BMJ open. 2013 Jan 1;3(5):e002762.

40. Sadati AK, Lankarani KB, Hemmati S. Patients' description of unexpected interactions: a critical ethnography of the quality of doctor-patient interactions in one educational hospital in Shiraz, Iran. Shiraz E-Medical Journal. 2016 Aug 31;17(7-8).

Original Article

EFFECT OF CITRULLUS LANATUS SEEDS (ETHANOLIC EXTRACT) ON NORMAL RENAL FUNCTIONS AND SERUM ELECTROLYTES OF ALBINO RATS

NeelofarYousaf Warraich,[1] Amtul Hafeez,[2] Wardah Siddique,[3] Fouzia Parveen,[4] Shahnaz Fatima,[5] Nazia Rashid,[6]

ABSTRACT

Objectives: To evaluate the effect of Citrullus lanatus seeds on normal renal functions and serum electrolytes for the improvement of kidney health in order to perform its functions in normal and stressful conditions.

Methods: The study was conducted at the Pharmacology Department, KEMU, Lahore and UVAS, Lahore in 2017. It was a randomized controlled trial (RCT). A sample size of 16 healthy albino wistar rats was taken. Rats were divided into two equal groups with 8 number of rats in each group and kept separately in metabolic cages. Group A was normal control group and given normal saline once a day orally. Group B was given the ethanolic extract of Citrullus lanatus seeds I/P 600 mg/kg/day.

Renal function tests (blood urea nitrogen, serum, and urine creatinine clearance) and serum electrolytes (Ca^{++}, Na^{+}, K^{+}, Mg^{++}) were evaluated along with effects on urinary volume, pH and specific gravity on day zero and day 14.

Results: Urinary output markedly increased in group B taking Citrullus lanatus seeds extract in comparison to normal control Group A with significant p-value < 0.001. Urinary pH of group B was improved significantly with p-value <0.001 in comparison to group A. Whereas, there was the insignificant difference in RFTS, serum electrolytes & urinary specific gravity of both groups at the end of the study.

Conclusion: The ethanolic extract of Citrullus lanatus seeds is helpful in maintaining kidney health to perform its functions properly.

Key Words: Citrullus Lanatus Seeds, Renal functions Tests, Serum Electrolytes

INTRODUCTION:

Kidneys are excretory and the secretory organ of the body responsible for the maintenance of the hemostatic state of the body by accomplishing the three major goals such as glomerular filtration, tubular resorption and tubular excretion[1] which are generally assessed by renal function tests. Electrolytes are minerals in body fluids that carry an electric charge and keep the heart, nerves, and muscles in proper function. As such, it is important to maintain a precise and constant balance of electrolytes to stay healthy. Our kidneys play an important role in ensuring that electrolyte levels remain invariant despite any change the body may undergo. Having excess or insufficiency of electrolytes in the body can be dangerous and in some cases fatal.

Sometimes kidneys functions get deteriorated depending upon the physical, chemical and biological circumstances that it faces. There is circumstantial evidence available now which shows rapid decline in kidney function with age, different chronic ailments and due to its exposure to toxic substances which lead to acute and chronic kidney failure. So, it is very important to maintain/ improve the health of kidneys to perform its functions in normal and stressful conditions.

[1] Assistant Professor Pharmacology, AMDC, Lahore.
[2] Assistant Professor Pharmacology, IM&DC, Sialkot.
[3] Assistant Professor Pharmacology, LMDC, Lahore.
[4] Assistant Professor Pharmacology, SMDC, Lahore.
[5] Assistant Professor Pharmacology, SMC, Narowal
[6] Assistant Professor Pharmacology, FMJU, Lahore.

The role of herbal remedies to boost normal health conditions is always considered effective. In recent years, an increasing number of people has chosen traditional remedies and products to improve their health conditions either alone or in combination with other herbal products.[2]

The nephroprotective role of different naturally occurring herbs is being studied to reduce stress caused by various reasons such as Aloe vera[3], Kabab chini[4], silymarin[5], rosemary, curcumin, propolis, ginger, black seeds, turmeric.

Citrullus lanatus fruit belongs to the Cucurbitaceae family Slight glance in past relieves the importance of Citrullus lanatus in traditional herbal medicine and remedies. It is not only used to overcome severe heat effects in the human body or quenching thirst, but its different parts such as roots, rind, pulp, and seeds are used for different purposes/treatments of different ailments because of its composition.[6] Seeds are the most ignored part of the fruit, unknown to the fact that it possess the maximal nutrient values in comparison to the whole fruit.[7]

Watermelon seeds are great sources of carbohydrates, protein (both essential and non-essential amino acids) and oil. These seeds comprise about 35% of protein, 50% of oil, and 5% of dietary fiber. Watermelon seed is also rich in micro- and macro-nutrients such as magnesium, calcium, potassium, iron, phosphorus, zinc. Watermelon seeds are a source of healthy fat (unsaturated), almost 90%, vitamins, antioxidants, minerals, proteins and phytochemicals (phenols and flavonoids). According to seed analysis by Okunrobo O et al.,(2012) different minerals are present in watermelon seed in different quantities such as magnesium (11.4 mg/kg), calcium (16.8mg/kg), potassium (7.8mg/kg), sodium (5.7 mg/kg) and zinc (1.2 mg/kg).[8]

Seeds have magical effects as a demulcent, pectoral tonic and; hepatoprotective and hypotensive agents. Seeds are used to treat bed wetting and UTI (urinary tract infection).[9] It is vermifuge; paralyzing tapeworms and roundworms. Their antimicrobial action is better than that of pumpkin seed oil.[10] They also possess analgesic, anti-inflammatory activity, anti-ulcerogenic and the hepatoprotective activity.[11]

METHODS:

The fresh fruit of Citrullus lanatus was purchased from the local fruit market of Lahore. The fruit was properly cut and seeds were separated. Proper identification of seeds was done by authorized personnel from GC University, Lahore. Seeds were properly washed and dried under sunlight for 3 days and then ground into fine powder using an electric blender. The ethanolic extract of Citrullus lanatus seeds was prepared[12] and dissolved in 5 ml distilled water. The dose for individual rat i.e. 600mg/kg was calculated. Doses were administered through feeding guage no. 16.

Adult healthy albino rats of male gender weighing 150-200 grams were purchased from the local market. Animals were numbered and kept in iron cages in individual groups, under good hygienic conditions, at room temperature under natural light and dark cycles so that to maintain the biological clock in the animal house of UVAS. Food and water were provided ad libitum.

Rats were divided into two experimental groups, containing eight rats in each group randomly. Group 1 was a healthy control group and 0.5 ml of distilled water was given orally once a day with a feeding tube (16 guage). Group 2 rats were given Citrullus lanatus seeds ethanolic extract in the dose of 600 mg/kg/day body weight orally with a 16 gauge feeding tube once daily. All the treatment was provided daily for 14 days. 24 hours of urine of rats was collected in a clean glass container and volume was measured in measuring glass beaker.

In a small amount of urine; its specific gravity, pH, glucose, and albumin were assessed by urine test strips of URIMED, Biotec Diagnostics UK Ltd.[13] The results were evaluated according to the change of

colors on the strips as mentioned on the strip leaflet.

The remaining urine was not centrifuged and poured into serum cups and stored in the research freezer (-20^{o}C) for analysis of urine creatinine later About 1-1.5 milliliters of whole blood was drawn by the cardiac puncture[9] using disposable syringes. The collected blood sample was transferred to labeled gel tubes and allowed to clot at room temperature for 30 minutes, then centrifuged at 3000 rev/min for 15 minutes.[14] The clear serum obtained was separated and shifted in serum cups and preserved at -20 ^{o}C till serum analysis was started. Lab tests were performed for analysis of RFTs and serum electrolytes. All the tests were performed on semiautomatic clinical chemistry analyzer, micro lab 300. Methods were followed as provided by manufacturer. Before the performance, the cuvettes and the frozen samples were warmed to desired temperature (37^{o}C).

All data was entered on graph pad prism version 8 for statistical analysis and p-value less than 0.05 was considered significant.

RESULTS:

Renal function tests including blood urea nitrogen, serum, and urine creatinine and creatine clearance were statistically insignificant in normal control group A and Citrullus lanatus seeds extract group B.

Similarly, electrolytes such as calcium, potassium, sodium and magnesium levels in serum of both groups were insignificant.

24 hours urinary output was significantly increased in group B in comparison to normal control group A. Urinary pH was improved in group B in comparison to group A whereas the insignificant difference was observed in the specific gravity of urine in both groups.

Table 1: comparison of RFTs among groups (n=8, mean± SEM)

RFTs	Group A	Group B
Blood Urea Nitrogen (mg/dl)	12.43±0.75	16.60±1.96
Serum Creatinine(mg/dl)	0.35±0.08	0.51±0.09
Urine Creatinine(mg/dl)	82.06±21.13	108.87±21.16
Creatinine Clearance(ml/min)	3.80±1.06	4.68±0.88

Group A: Normal control group, Group B: Citrullus lanatus seeds extract group

Table 2: Comparison of serum electrolytes among groups (n=8, mean± SEM)

Serum electrolytes(mm0l/l)	Group A	Group B
Serum sodium	139.70±6.50	134.30±8.01
Serum potassium	4.86±0.33	4.69±0.21
Serum calcium	8.94±1.38	8.17±1.20
Serum magnesium	1.98±0.12	1.91±0.10

Group A: Normal control group, Group B: Citrullus lanatus seeds extract group

Table 3: Comparison of urinary parameters among groups (n=8, mean± SEM)

Urinary parameters	Group A	Group B
24hrs urinary output (ml)	23.00±0.92	31.50±3.38
Specific gravity	1.02±0.01	1.02±<0.01
pH	6.50±0.37	5.65±0.17

Group A: Normal control group, Group B: Citrullus lanatus seeds exrtract group.

DISCUSSION:

Citrullus lanatus seeds are a combination of various components that are beneficial as well protective for kidneys. Electrolytes and various minerals content in the seeds are the main sources to improve functions of the kidney and deteriorate its functions in stressful conditions that may lead to acute or chronic renal failure. In our current study, we tried to evaluate the effect of Citrullus lanatus seeds in order to improve kidney health. We observed that there was no effect of Citrullus lanatus seeds extract on blood urea nitrogen when administered alone to healthy rats. This effect is in accordance with a previous study in which the effect of Citrullus lanatus seeds was evaluated in normal healthy rats.[15] But over the period of time, there was no significant difference within group A at day 0 and 14 but significant difference was present within

group B at day 0 and day 14 which shows that seeds extract improves the Blood urea nitrogen in normal healthy rats. The seeds of Citrullus lanatus neither increased nor decreased the serum creatinine and urine creatinine and creatinine clearance in normal healthy rats. No literature is found in support of the effect of Citrullus lanatus seeds on creatinine levels and creatinine clearance in normal healthy rats.

No change in serum potassium and magnesium levels of group B was noticed at day 14 in comparison to normal control group A. This effect was in accordance with a previous study in which no effect was seen in serum potassium values after using Citrullus lanatus seed extract.[15]

No change in serum calcium and sodium levels of group B was noticed at day 14 in comparison to normal control group A which shows that Citrullus lanatus seed extract kept the serum calcium and sodium levels within the normal range in healthy rats. Over a period of time, there was no significant difference within group an on day 0 and 14 but a significant difference was present within groups B on day 0 and day 14.

In group B diuretic effect of the Citrullus lanatus, seed extract was observed whereas urinary specific gravity and pH remained unchanged showing that seeds extract helped to maintain them in the normal range.

CONCLUSION:

According to these findings, it is concluded that the ethanolic extract of Citrullus lanatus seeds is helpful in maintaining kidney health to perform its functions properly.

ACKNOWLEDGMENTS:

I am really thankful to my supervisor Dr. Zujaja Zaheer for her kind supervision. I want to pay my gratitude to my parents and my dear husband.

REFERENCES:

1. Hall JE. Hemostasis and blood coagulation: Guyton and Hall Textbook of Medical Physiology. 13th ed. Philadelphia, PA: Elsevier. 2016.
2. Ahmad A, Husain A, Mujeeb M, Khan SA, Najmi AK, Siddique NA, Damanhouri ZA, Anwar F. A review on therapeutic potential of Nigella sativa: A miracle herb. Asian Pacific journal of tropical biomedicine. 2013 May 1;3(5):337-52.
3. Virani SH, Bhatt SH, Saini MA, Saxena KK. Aloe vera attenuates gentamicin-induced nephrotoxicity in wistar albino rats: histopathological and biochemical changes. Asian J Pharm Clin Res. 2016;9(1):113-7.
4. Ahmad QZ, Jahan N, Ahmad G. Nephroprotective effect of Kababchini (Piper cubeba) in gentamycin-induced nephrotoxicity. Saudi Journal of Kidney Diseases and Transplantation. 2012 Jul 1;23(4):773.
5. Ghaznavi H, Mehrzadi S, Dormanesh B, Tabatabaei SM, Vahedi H, Hosseinzadeh A, Pazoki-Toroudi H, Rashidian A. Comparison of the protective effects of melatonin and silymarin against gentamicin-induced nephrotoxicity in rats. Journal of evidence-based complementary & alternative medicine. 2016 Oct;21(4):NP49-55.
6. Rahman H, Priyanka P, Lavanya P, Srilakshmi N, Kumar PR. A review on ethno botany, phytochemistry and pharmacology of Citrullus lanatus L. International Research Journal of Pharmaceutical and Applied Sciences. 2013 Apr 28;3(2):77-81.
7. Mehra M, Pasricha V, Gupta RK. Estimation of nutritional, phytochemical and antioxidant activity of seeds of musk melon (Cucumismelo) and water melon (Citrullus lanatus) and nutritional analysis of their respective oils. Journal of Pharmacognosy and Phytochemistry. 2015 Feb;3(6):98-102.
8. Lucky OO, John UO, Kate IE, Peter OO, Jude OE. Quantitative determination, Metal analysis and Antiulcer evaluation of Methanol seeds extract of Citrullus lanatusThunb (Cucurbitaceae) in Rats. Asian Pacific Journal of Tropical Biomedicine. 2012 Jan 1;2(3):S1261-5.
9. Kumari A, Rao J, Kumari J, Sharma N, Jain P, Dave V, Sharma S. Analgesic activity of aqueous extract of Citrullus lanatus peels.

Advances in Pharmacology and Pharmacy. 2013 Dec;1(3):135-8.
10. Aruna A, Vijayalakshmi K, Karthikeyan V. In vitro Antioxidant screening of Citrullus lanatus leaves. INTERNATIONAL JOURNAL. 2014;1:01.
11. Erhirhie EO, Ekene NE. Medicinal values on Citrullus lanatus (watermelon): pharmacological review. International Journal of Research in Pharmaceutical and Biomedical Sciences. 2014;4(4):1305-12.
12. Padzys GS, Ondo JP, Omouendze LP. Impact of Gnetum africanum and Amaranthus rectroflexus Plant Food on Urea, Creatinine and Plasma Electrolytes. Journal of Agricultural Science. 2015 Feb 1;7(2):174.
13. Urine test strips of URIMED, Biotec Diagnostics UK Ltd.
14. Khaki A, Fathiazad F, Nouri M, Khaki AA. Effect of citrullus lanatus seeds extracts on serum total testosterone in rat. Crescent Journal of Medical and Biological Sciences. 2014;1(1):25-27
15. Garuba T, Sabiu S, Ambali IA, Feyijin IB. toxicological implications of acute and repeated dose administrations of hydroethanolic extract of citrullus vulgaris seeds in wistar rats. Annales of West University of Timisoara. Series of Biology. 2017;20(1):49.

Original Article

COMPARISON OF THE RESULTS OF ANTERIOR NASAL PACKING VERSUS WITHOUT ANTERIOR NASAL PACKING FOR BETTER MANAGEMENT OF SEPTOPLASTY

Zubair Iqbal Bhutta[1], Ali Husnain Sheikh[2], Muhammad Dawood Saleem[3], Shuman Roy[4]

ABSTRACT

Objectives: The rationale of this study was to compare the results of anterior nasal packing versus without anterior nasal packing for better management of septoplasty.

Methods: This study was conducted in the department of ENT, Akhtar Saeed Trust Hospital Lahore on 220 patients who were randomly divided into two equal groups. Septoplasty was performed by a single team of surgeons and patients were followed till 6 weeks for evaluation of post-septoplasty complications like pain, septal hematoma, and bleeding. Data was collected on a specially designed proforma (attached) and analyzed on SPSS version 20.

Results: In this study of 220 patients, there were 139 males and 81 females with age range from 18 to 45 years. The mean age of 139 (63.2%) male patients and 81 (39.1%) female patients was 25.90 ± 5.974. The female to male ratio was 1:1.7. In group "A" consisting of 67 (60.9%) male and 43 (39.1%) female patients the mean age was 25.89 ± 5.97. Similarly, group "B" consisting of 72 (65.5%) male and 38 (34.5%) female patients the mean age was 25.92 ± 6.194. In group "A" (with anterior nasal packing) after septoplasty 51 (46.4%), 45 (40.9%) and 14 (12.1%) patients described mild, moderate and severe pain respectively on visual analog scale. In group "B" (without anterior nasal packing) 18 (16.4%) had no pain and 92 (83.6%) patients had mild pain during the first 24 hours post-operatively (P-value < 0.05). During septoplasty 03 (2.75) patients from each group developed primary heamorrhage of grade I. Reactionary haemorrhage was noted in 27 (24.5%) patient in group A and 8 (7.30%) in group B. Secondary heamorrhage was noted in 26 (23.6%) patients in group A and 04 (3.6%) in group B with statistically significant difference (P-value < 0.05).

Conclusion: On the basis of results in two groups, post-septoplasty complications rate of pain, primary & secondary haemorrhage was less in group B (without anterior nasal packing) than in group A (with anterior nasal packing). Septal hematoma formation was rare in both groups and statistically was not significant. On the basis of the result obtained from this study, it is recommended that septoplasty operation without anterior nasal packing can be used confidently to achieve the best surgical results.

Key Words: Nasal septum, septoplasty, Nasal Packing

INTRODUCTION

It is a common and traditional practice to do anterior nasal packing after septoplasty to prevent bleeding, septal haematoma, synechiae and to get a midline position of septal cartilage and coaptation of the mucoperichondrial&mucoperiosteal flap. Anterior nasal packing causes nasal pain, headache, epiphoria, dryness of mouth, disturbed sleeping pattern, blocked ears, earache, gag and difficulty in swallowing, and prolong hospital stay.[1] Although these are temporary sufferings and revert after removal of anterior nasal packing but a cause of considerable nuisance to the patient during the period of anterior nasal packing and its removal after 24 - 48 hours.[2] Considerable bleeding may start during anterior nasal packing removal due to injury to the nasal mucosa and becomes difficult to control and require anterior nasal packing to be done again. The patient may complain of severe discomfort and can request for the removal of packing under general

[1] Professor ENT, AMDC, Lahore.
[2] Associate Professor ENT, AMDC.Lahore
[3] Assistant Professor ENT AMDC, Lahore.
[4] Senior Registrar ENT, AMDC, Lahore

anaesthesia. The injured mucosa of the septum and turbinates adhere together to form synechiae formation in the nasal cavities in the post-operative period.[3] These adhesions (synechiae) cause nasal obstruction, crusting, nasal pain, pooling of nasal secretions, ultimately infection and bleeding from the nasal cavities. The patient return with initial symptoms and consequent failure of surgery.[4] Paraffin granuloma formation result by anterior nasal packing on the nasal septum. Tight nasal packing to prevent septal haematoma, bleeding and stabilization of septal cartilage, in the midline position increases chances of septal cartilage necrosis due to reduced blood supply leading to septal perforation.[5]

A rare condition, toxic shock syndrome; occurs after septal surgery with nasal packing. It is caused by staphylococcal (sometimes streptococcal) bacteremia and the patient develops nausea, vomiting, purulent secretions, hypotension and body rash.[1,6] Pragmatic benefits without nasal packing septoplasty, do not cause nasal obstruction, nasal pain, headache, dryness of mouth, blockage of ears, earache, gag, difficulty in swallowing, epiphora and disturbed sleeping pattern.

In this context, different studies and literature suggest that anterior nasal packing is not necessary after septoplasty to prevent post-operative nasal bleeding and septal haematoma.[7,9] Therefore the routine use of anterior nasal packing following septoplasty is not justified.[9]

METHODS

This study was conducted in the ENT department of Akhtar Saeed Trust Hospital from July 2017 to June 2019. It was a randomized control trial. Non- probability purposive sampling technique was used.

The sample size has been calculated (Maeed and Al-Shehri., 2011) using the expected percentage of post-operative pain in group A (with an anterior nasal packing) 28.60% and 11.40% in group B (without anterior nasal packing) at 90% power of study and 5% level of significance. In this study, 220 patients were allocated randomly into groups A and B comprising 110 patients in each group. Patients were included in the study regardless of the type of septal deviation, patients of either sex between the ages of 18 to 45 years were incorporated in this research work.

All those patients who were submitted to revision surgery, had associated nasal surgeries (e.g.; Septo-Rhinoplasty), hypertensive, had coagulation disorders (PT > 14sec., APTT> 35sec., INR> 1.2) were excluded. Each patient was randomly allocated into two groups as Groups A (110 patients) and group B. (110 patients) by using the balloting method.

All collected data were analyzed using SPSS version 20. Descriptive statistics, mean and ± S.D was used for quantitative data like age (years). Frequencies and percentages were calculated for qualitative data like gender and post-operative complications. Independent sample t-test was applied to compare the intensity of postoperative pain on the visual analog scale in both groups. Chi-square test was applied to compare the presence of postoperative haemorrhage & septal haematoma in both groups.

RESULTS:

In this study, the average age of patients was 25.90 ± 5.974 years. The minimum age of patients was 18 and the maximum age of patients was 45 years. The mean age of patients in Group A and Group B was 25.89 ± 5.773 and 25.92 ± 6.194 years respectively. There was no statistical difference in age in group A and group B, p-value > 0.05 (0.793). In group A with anterior nasal packing, there were 67 (60.90 %) males and 43 (39.10 %) females and in group B without anterior nasal packing, 72 (65.5% %) males and 38 (34.5 %) female patients. The female to male ratio was 1:1.7. There was no statistical difference in gender in 'group A and group B, p-value > 0.05(0.793). Gender distribution showed that there were 139 (63.2%) patients were

male and 81 (36.8%) were female. Male B[a] = Pain measured in group B (without anterior nasal packing)

After septoplasty, 51 (46.4%), 45 (40.9%) and 14 (12.7%) patients described mild, moderate and severe pain respectively in group A (with an anterior nasal packing), Table 1.

While in group B. 18 (16.4%) patients were free of pain and mild pain complained by 92 (83.6 %) after septoplasty. There was a statistically significant difference between group A and group B (p-value < 0.05). After patients were dominating female patients

24 hours pain intensity shifted from mild to moderate and severe levels 10 (9.1%), 18 (16.4%) and 82 (74.5%) respectively in group A. on the other side in group B, 93 (84.5%) were free of pain and 17 (15.5%) complained mild pain on visual analog scale. There was a statistically significant difference between group A and group B (p-value < 0.05).

Table 1: Comparison of Pain in Group A and Group B

			Pain				
Time	**Group**		**No Pain**	**Mild Pain**	**Moderate Pain**	**Severe Pain**	**p-Value**
After Nasal Packing	A	Frequency	0	51	45	14	0.00*
		Percent	0%	46.4%	40.9%	12.7%	
	B	Frequency	18	92	0	0	
		Percent	16.4%	83.6%	0%	0	
After 24 Hours	A	Frequency	0	10	18	82	0.00*
		Percent	0%	9.1%	16.4%	74.5%	
	B	Frequency	93	17	0	0	
		Percent	84.5%	15.5%	0%	9%	
During pack removal after 48 Hours	A	Frequency	0	0	38	72	0.00*
		Percent	0%	0%	34.5%	65.6%	
	B[a]	Frequency	100	10	0	0	
		Percent	90.9%	9.1%	0%	0%	
01 Weeks	A	Frequency	14	96	0	0	0.00*
		Percent	12.7%	87.3%	0%	0%	
	B	Frequency	110	0	0	0	
		Percent	100%	0%	0%	0%	
02 Weeks	A	Frequency	43	67	0	0	0.00*
		Percent	39.1%	60.9%	0%	0%	
	B	Frequency	110	0	0	0	
		Percent	100%	0%	%	0%	
03, 04, 05 & 06 weeks	A	Frequency	110	0	0	0	0.00*
		Percent	100%	0%	0%	0%	
	B	Frequency	110	0	0	0	
		Percent	100%	0%	0%	05	

* p - value< 0.05

Table 2 Septal Haematoma Formation in Group A and Group B

		SeptalHaematoma		
		No Haematoma	**Haematoma**	**Total**
Group A	Frequency	107	03	110
	Percent	97.3	2.7	100.0
Group B	Frequency	106	04	110
	Percent	96.4	3.6	100.0
P- Value		0.083	0.045	0.320

*p - value > 0.05

After 48 hours, anterior nasal packing was removed in group A patients and pain levels dramatically shifted towards moderate and severe pain in 38 (34.5%) and 72 (65.5%) patients respectively. While 100 (90.9%) patients in group B were free of pain and only 10 (9.1%) patients had mild pain. There was a statistically significant difference between group A and group B (p-value < 0.05).

After one week 110 (100%) patients were free of pain in group B (without anterior nasal packing). 14 (12.7%) patients in group A were free of pain and 67 (60.9%) patients had mild pain. There was a statistically significant difference between group A and group B (p-value < 0.05).

After two weeks, all patients in group B (without anterior nasal packing) and 43 (39.1%) in group A (with an anterior nasal packing) were free of pain while 67 (60.9%) patients had mild pain in group A (with anterior nasal packing). There was a statistically significant difference between group A and group B (p-value < 0.05). After 03, 04, 05 & 06 weeks all patients in group A and group B were free of pain.

In group A (with an anterior nasal packing) 03 (2.7%) patients and in group B (without anterior nasal packing) 04 (3.6%) patients developed septal haematoma, table 2. There was no statistically significant difference between group A and group B (p-value > 0.05).

During septoplasty, 03 (2.7%) patients from each group developed primary haemorrhage of grade I, table 3. Reactionary haemorrhage was noted in 27 (24.5%) patients in group A and 8 (7.3%) in group B. Secondary haemorrhage was noted in 26 (23.6%) patients in group A and 04 (3.6%) in group B. There was a statistically significant difference between two groups in, reactionary and secondary haemorrhage (p-value < 0.05).

Table 3: Bleeding in Group A and Group B

	No Bleeding	**Grade I Bleeding**	**Grade II Bleeding**	**Grade III Bleeding**	**Grade IV Bleeding**
Primary (Group A)	107	3	0	0	0
Reactionary (Group A)	83	27	0	0	0
Secondary (Group A)	84	26	0	0	0
Primary (Group B)	101	3	0	0	0
Reactionary (Group B)	102	8	0	0	0
Secondary (Group B)	106	4	0	0	0

DISCUSSION

In this study, the total number of the patient was 220. Patients were between the age ranges of 18 - 45 years. The mean age of patients was 25.90 ± 5.974 years with 139 (63.2%) male and 81 (36.8%). female patients. There was no statistically significant difference between age and gender in group A and group B (p-value > 0.05). In this study, the female to male ratio was 1: 1.7. This higher proportion of male patients is also reported in literature [3].In this study, all (220) patients were randomized into two equal groups by balloting method. Group A comprised of 110 patients and was subjected to pack with anterior nasal packing after septoplasty. While group B also comprising of 110 patients was managed without anterior nasal packing post-operatively. We documented and correlated post-operative data in terms of pain, bleeding and septal haematoma in group A and group B. Data of Pin description was collected from patients on visual analog scale reading from 0 to 10 level at 24 and 48 hours, then on 7, 14. 21, 28, 35 and 42 days after procedure.After septoplasty, nasal pain at 24 and 48 hours was higher in group A (Patients with anterior nasal packing) on VAS than group B (Patients without anterior nasal packing). In group A, mild, moderate and severe pain complained by 31 (46.4%), 15 (40.9%) and 14 (12.7%) patients respectively in first 24 hours after septoplasty. At the end of 48 hours during the removal of anterior nasal packing pain level in group A shifted from mild, moderate and severe stage to moderate and severe level in 38 (34.5%) to 72 (65.6%) patients respectively reporting a value greater than 7 on visual analog scale - severe pain on visual analog scale. On the other side, after 48 hours 100 (90.9%) patients in group B were free of pain and remaining 10 (9.1%) had mild pain. In literature, similar results are present in which high grades of postoperative pain were narrated by patients in first 24 hours and higher upon removal of the pack in the anterior nasal packing group [4]. Their stated grades on visual analog scale were significantly more than those without anterior nasal packing septoplasty. Patients with anterior nasal packing septoplasty ominously showed more tears, headache and complained disturbed sleep patterns. One more study depicts similar data in which post-operative pain was evaluated after septoplasty in 697 patients [5]. This study exhibited that patients packed with anterior nasal packing complained more pain than those without anterior nasal packing after. septoplasty. In our study, patients without anterior nasal packing were 90.9% free of pain and no pain recorded in a single patient after 1 week. However, patients in group A with anterior nasal packing complained nasal pain till the end of 3rd week. Statistically significant differences persisted throughout the study till the end of 3 weeks between two groups (p-value > 0.05). In this study, patients in group A (with anterior nasal packing) had minor oozing after septoplasty and more oozing upon removal of anterior nasal packing after 48 hours. This oozing was managed conservatively by nose pinching and vasoconstrictor drops in 83 (75.3%) patients. Remaining 27 (24.7%) patients had grade 1 reactionary haemorrhage and 6 patients were repacked with anterior nasal packing for next 12 hours. On the other hand, in group B, reactionary haemorrhage of grade I was noted in 8 (7.2%) patients. They were managed with vasoconstrictor drops and anterior nasal packing was not done even in a single patient. Such observations are also described in the literature [7]. Post-operative reactionary haemorrhage up to 7.7% had been reported. Half of these patients were managed with conservative treatment and remaining half were repacked to control the reactionary haemorrhage. Their statistical data was significant with and without anterior nasal packing after septoplasty. In addition, 26 (23.6%). cases of secondary haemorrhage in group A and 04 (3.6%) cases in group B came back on 7th and 9th day and all were packed with anterior nasal packing for next 12 hours. In group B without anterior nasal packing, post-

operative oozing was minimal on the first day compared to patients with nasal packing. Five patients came back with minor oozing within 24 48 hours on 3rd day of operation. This oozing was managed with nose pinching and vasoconstrictor drops and send back to home with assurance. In group A and group B, patient did not come back with secondary haemorrhage of grade II, Ill and IV after septoplasty. 84 (76.4%) patients in group A and 106 (96.4%) patients in group B did not report any problem till the end of this study. Similar results also have been reported in literature [8]. After septoplasty, patients in group B (without nasal packing) were discharged on the same day compared to patients in group A (with anterior nasal packing) who were discharged on second and third day. In this study. septal haematoma was a rare complication after septoplasty. Only 03 (2.7%) patients in group A and 04 (3.6%) patients in group B developed septal haematoma (p-value > 0.05). The septal haematoma was drained and nasal cavity packed for 12 hours. These results show that anterior nasal packing has no substantial role to prevent the septal haematoma after septoplasty. These results correlate with a study[13] in which only one patient with anterior nasal pack 1H, developed septal hematoma post-operatively. A meta-analysis study conducted by Ranglawala[3] reported that 10' and 07 out of 948 patients developed septal haematoma in packed and non - packed groups respectively. Consequently if anterior nasal packing is certainly effective then there should be no septal haematoma formation in anterior nasal packing septoplasty and definitely should have septal haematoma formation in all patients without anterior nasal packing.

CONCLUSION

On the basis of findings in this study, group B (without anterior nasal packing) had an early pain free rate (at day 1) and less complications (such as primary & secondary haemorrhage) compared with group A (with anterior nasal packing). The septal hematoma formation is statistically insignificant in both groups. In the future, we can perform septoplasty without anterior nasal packing to achieve early pain - free rates, fewer complications, less hospital stay and may be higher satisfaction of our patients.

REFERENCES

1. Al-Raggad DK, El-Jundi AM, Al-Momani OS, Al-Serhan MM, Nawasrah OO, Qhawi MA, Husban AM. Suturing of the nasal septum after septoplasty, is it an effective alternative to nasal packing?. Saudi medical Journal. 2007 Oct;28(10):1534.
2. Awan MS, Iqbal M. Nasal packing after septoplasty: a randomized comparison of packing versus no packing in 88 patients. Ear, Nose & Throat Journal. 2008 Nov;87(11):624-627.
3. Banglawala SM, Gill M, Sommer DD, Psaltis A, Schlosser R, Gupta M. Is nasal packing necessary after septoplasty? A meta-analysis. In International forum of allergy & rhinology 2013 May; 3(5);418-424.
4. Bernardo MT, Alves S, Lima NB, Helena D, Condé A. Septoplasty with or without postoperative nasal packing? Prospective study. Brazilian Journal of Otorhinolaryngology. 2013 May;79(4):471-474.
5. Cole P, Chaban R, Naito K, Oprysk D. The obstructive nasal septum: effect of simulated deviations on nasal airflow resistance. Archives of Otolaryngology–Head and Neck Surgery. 1988 Apr;114(4):410-412.
6. Cukurova I, Cetinkaya EA, Mercan GC, Demirhan E, Gumussoy M. Retrospective analysis of 697 septoplasty surgery cases: packing versus trans-septal suturing method. Acta Otorhinolaryngologica Italica. 2012 Apr;32(2):111.
7. Eski E, Yilmaz I. Septoplasty without Nasal Packing: Functional Outcomes and Complications, A Prospective Clinical Study. Journal of Otolaryngology - ENT Research, 2015 Sep; 3(2) : 00062.
8. Hafeez M, Ullah I, Iqbal K, Ullah Z. Septoplasty without nasal packing. Gomal Journal of Medical Sciences, 2010;8 (2): 141 - 142.

9. Sreenivasulu M, Hemanth V, Durgaprasad V, Sowmya L. Septoplasty with and without nasal packing: A comparative study. Journal of Evidence Based Medicine and Healthcare. 2016 May; 3 (36): 1765-1767.
10. Reitzen SD, Chung W, Shah AR. Nasal septal deviation in the pediatric and adult populations. Ear, Nose and Throat Journal. 2011 Mar;90(3):112-115.
11. Mladina R, Čujić E, Šubarić M, Vuković K. Nasal septal deformities in ear, nose, and throat patients: an international study. American journal of otolaryngology. 2008 Mar 1;29(2):75-82.
12. ALI MAEED S AL-SHEHRI MD. Assessment of complications of nasal packing after septoplasty. The Medical Journal of Cairo University. 2011;79(2).
13. Mane RS, Patil B, Mohite A. Comparison of septoplasty with and without nasal packing and review of literature. Indian Journal of Otolaryngology and Head & Neck Surgery. 2013 Aug;65(2):406-408.
14. Kim J, Kim SW, Kim SW, Cho JH, Park YJ. Role of the sphenoidal process of the septal cartilage in the development of septal deviation. Otolaryngology--Head and Neck Surgery. 2012 Jan;146(1):151-155.

Review Article

PHARMACOLOGICAL ACTIONS OF NIGELLA SATIVA (KALONJI)

Muhammad Usman Bashir[1] and Hamid Javaid Qureshi[2]

ABSTRACT

Nigella Sativa (Kalonji) is extensively grown in many countries including Pakistan. These have been used for therapeutic purposes for centuries.

Its effects are due to its constituent's thymoquinone and thymohydroxyquinone. Thymoquainone reduces the duration of tonic-clonic seizures. Nigella Sativa possesses anxiolytic and neuroprotective effects. Its seeds extract reduces systolic and diastolic blood pressures and blood lipids. Reduction in blood glucose, leucocyte and platelet counts has been reported. Thymoquinone has gastroprotective and hepatoprotective effects. Its seeds are potential immunosuppressive, cytotoxic, antibacterial and antiprolifertive agents. Aqueous extract of Nigella Sativa increases weight of reproductive organs, spermatogenesis, and secretion of seminal vesicles and prostate. This extract also has anti-inflammatory, analgesic, antipyretic and antioxidant effects.

To conclude, the seeds of Nigella Sativa in addition to their use as spices possess a variety of Pharmacological actions.

KeyWord: Nigella Sativa, Blood platelets, Spermatogenesis, Prostate

INTRODUCTION:

Nigella sativa is extensively grown all over the world including Pakistan, India, Iran, Afghanistan, and many Arab countries. Its seeds are used as a condiment in Middle Eastern and South Asian cuisine. The seeds impart flavor to curries, vegetable stews, and pulses. The scientific name, Nigella Sativa, is a derivative of the Latin "niger" (black). It is known by a variety of names in English such as black cumin, fennel flower or Roman coriander. It is called "siyahdaneh" in Persian, "habbat-ul-barakah" in Arabic and "kalonji" in Urdu,.[1]

Numerous references to kalonji seeds can be found in ancient medical texts and religious scriptures. Prophet Muhammad (peace be upon him) said, "Use this Black Seed regularly, because it is a cure for every disease, except death." An Assyrian Herbal book has described black seed as a remedy for stomach related problems and also as a medicine for external problems like those of ears, eyes, mouth, and skin (e.g. herpes, sores, and rashes).

Nefertetes and Cleopatra used it for its healthy and rejuvenating qualities. Pliny described its myriad of uses like therapy for scorpion stings, snake bites, skin rashes, abscesses and tumors.[3-4]

TRADITIONAL USES:

Nigella sativa was used for therapeutic purposes both in herb and oil-pressed forms for centuries, in Middle East, Asia, and Africa. Traditionally, it was used as a remedy for a number of conditions related to respiratory, gastrointestinal, renal and hepatic functions, and as circulatory and immune system support apart from generalized health.

It was usually consumed with food or in combination with honey. In the 'UnaniTibb', Nigella sativa was considered as a useful cure for various ailments. A suspension made from its seeds was considered useful in the treatment of dyspepsia, anorexia, diarrhea, amenorrhea, parasitic infestations, and skin lesions. Ingestion of roasted seeds provided anti-emetic effect.[1-5]

[1] Associate Professor Physiology, CIMS, Multan.
[2] Professor Physiology, AMDC, Lahore.

PLANT MORPHOLOGY:

Nigella Sativa is a member of the Ranunculaceae family with about 14 species in its genus. Amongst these species, Nigella sativa is extensively investigated for medicinal properties.[6,7]

It is an annual flowering plant, found in southwest Asia. The average height of this plant is 20-30 cm, and its leaves are finely divided (Fig. 1). It has a range of colorful flowers. The fruit is a capsule comprising of many unified follicles, containing abundant seeds. It has a pungent taste and smells faintly of strawberries. The seeds contained in the fruit are used for medicinal purposes.[8]

Fig. 1: The seeds (right) and flowering plant (left) of Kalonji.

The majority of the studies involved the seeds of the plant. Phytochemical studies have been done on the essential oil[9], fixed oil[10], methanolic extract[11], aqueous extract[12], ethanolic extract[13,14] and n-hexane extract[14] obtained from the seeds.

It is chemical composition reveals that Nigella Sativa has: fixed oil (35.6-41.6%), volatile oil (0.5-1.6%), amino acids, proteins (22.7%), alkaloids, saponins, toxic glycosides, amongst many other compounds. These also contain minerals like iron, sodium, copper, calcium and zinc and vitamins e.g. ascorbic acid, folic acid, thiamine, niacin, and pyridoxine. They also yield fatty acids esters (e.g. dehydrostearic acid, palmitic acid and oleic acid,) and unsaturated hydroxy ketones, sterylesters, sterylglucosides, acylatedsterylglucosides, lipase, phytosterols, and β-sitosterols.[1]

Ghoshehet al.[15] after carrying out HPLC (high-performance liquid chromatography) analysis of Nigella sativa concluded that the concentration of thymoquinone and thymohydroquinone (THQ, termed 'Nigellone' by earlier workers) and some other constituents depended upon the conditions of storage of the seeds.

PHARMACOLOGICAL ACTIONS OF NIGELLA SATIVA:

Nigella sativa possesses a large number of pharmacological actions and numerous studies have been done so far on various properties of this plant.

Thymoquinone shortened the time span of tonic-clonic fits.[16] Aqueous and methanolic extracts produced significant alteration in the general behavioral patterns and reduction in spontaneous motor activity and body temperature, suggesting a central nervous system (CNS) depressant action of Nigella sativa.[11] Nigella sativa was also found to possess anxiolytic and neuroprotective effects in rats.[17,18]

In an eight weeks study, systolic blood pressure (SBP) values in patients with hypertension receiving Nigella sativa seed extract supplementation were found to be significantly lower when compared with the control group. In addition, the reduction in blood pressure was found to be dose-dependent. A significant decrease in total cholesterol and LDL-cholesterol were also seen.[19] Another study revealed that Nigella sativa also possessed blood pressure-lowering properties which were similar to nifedipine. A Nigella sativa extract given orally had significantly increased diuresis after 15 days of treatment in spontaneously hypertensive rats. Thymol, one of its active ingredients, reduced blood pressure by blocking calcium channels.[7] Supplementation of the diet with seed extract, caused homogenous cardiac hypertrophy and enhanced cardiac contractility in normal rats.[20]

In one study, Nigella sativa fixed oil was administered orally to rats for 12 weeks.

Total cholesterol, total leukocyte count (TLC), platelets and serum glucose were found to be decreased.[21] In another study, Thymoquinone resulted in a significant decrease in blood cholesterol, low-density lipoprotein (LDL) levels and triglycerides.[22]

In hamsters, a significant reduction in serum glucose and an increase in insulin level was noted following treatment with oil of Nigella Sativa.[23] El-Mahmoudy et al. demonstrated β-cell conserving function of thymoquinone using diabetic rat model. The hyperglycemia was significantly diminished in thymoquinone treated rats.[24] Recently, in a Pakistani study also, Nigella sativa was found to possess hypoglycemic properties.[25]

In minute concentrations, cells sensitized by the secretagogues antigen demonstrated reduced histamine release with Nigellone.[26]

Effects of thymoquinone and nigellone were investigated on the trachea (antispasmodic effect) in rats. Thymoquinone minutely modified the ciliary clearance rate whereas nigellone markedly increased it.[27] In another study, intraperitoneal injection of thymoquinone resulted in a significant reduction of allergen-induced eosinophilic lung inflammation while decreasing the activity of goblet cells.[28]

Thymoquinone and oil of Nigella sativa also showed gastroprotective activity.[29] The gastroprotective activity of Nigella sativa was also established against alcohol-induced gastric injury, acidity of the stomach and experimentally induced colitis.[30-32]

Significant protection was exhibited against carbon tetrachloride mediated hepatotoxicity by Thymoquinone given orally.[33] When comparing hepatoprotective effects of Thymoquinone and Silybin against the toxicity produced by tetra-butyl hydroperoxide (TBHP) in rat hepatocytes, it was found out that even though both compounds prevented TBHP-induced toxicity, thymoquinone resulted in lesser enzyme leakage than silybin.[34] In another study, hepatic ischemia was induced in rats, followed by reperfusion. Nigella sativa was administered intraperitoneally, both before inducing ischemia and before reperfusion. The levels of various liver enzymes were significantly lower in Nigella sativa treated group compared to control group.[35]

It was found that in the diabetic rabbit model, treatment with Nigella sativa increased the red blood cells, neutrophil percentage, and leukocyte counts.[36] Anti-angiogenic activity on endothelium of aorta in rats was also observed.[37]

Nigella sativa oil possesses immunomodulatory and immunotherapeutic properties.[38,39] It is able to improve age-related decline in functions of T cells. Supplementation with the Nigella sativa oil in healthy elderly people has been shown to enhance immune response.[40] It could be regarded as potential cytotoxic and immunosuppressive agent.[41]

Thymoquinone's concentration-dependent anti-proliferative actions were investigated in neoplastic and normal cell lines. It was found to impede proliferation.[42] In osteosarcoma and human colon neoplastic cells it also induced G1 phase cell-cycle arrest.[43-45] Thymoquinone also offers some protection against human neuroblastoma and androgen-dependent human prostate cancer.[46,47]

Treatment of rats with ethanolic extract decreased deposits of Calcium oxalate.[48] Aqueous extract of Nigella sativa significantly increased the size of reproductive organs, sperm motility, spermatogenesis and secretions of seminal vesicle and prostate.[49]

In S. aureus and E. coli infected mice, both essential oils and crude extracts of Nigella sativa exhibited anti-bacterial effects.[50] Similarly, thymohydroquinone (THQ) and thymoquinone (TQ) were also found to possess antibacterial effects against Pseudomonas aeruginosa, Escherichia coli, and other bacteria.[51]

Nigella sativa oil showed a strong anti-viral action against infection with cytomegalovirus.[52] In another study, antiviral activities against laryngotracheitis virus were exhibited by both Nigella sativa and green tea.[40] Chloroform and Methanol extracts of the Nigella sativa showed strong

anti-fungal actions against the hospital and standard Candida albicans strains. Aqueous extract of Nigella sativa, however, showed no effect.[53] Nigella sativa oil also produced significant effects on parasitemia in Trypanosomabrucei-infected rats.[54]

Antioxidant properties of thymoquinone have been explained through different mechanisms in several studies.[55-56]

Nigella sativa significantly declined the paw edema induced with carrageenan. Analgesic activity was also tested in mice. The extract produced a significant analgesic effect in mice as seen by the increase in reaction time when exposed to hot plate. However, its crude suspension showed no effect on pyrexia induced by yeast.[12]

The effect of methanolic and aqueous extracts of black cumin seeds was investigated on pain response in albino mice. Methanolic and aqueous extracts were injected intraperitoneally to the mice and hot plate reaction time was estimated. The observations suggested that both the extracts possessed analgesic and CNS depressant effects.[11]

Effectiveness of thymoquinone and Nigella sativa oil against rheumatoid arthritis was evaluated in rats. Oral thymoquinone was given to rats in a dose of 2.5mg/Kg. The control group received only the normal saline while the reference group was given standard drug methotrexate. Thymoquinone was found to suppress adjuvant-induced arthritis clinically and radiologically, significantly, as compared with the control and reference groups.[57]

It can be concluded that seeds of Nigella Sativa in addition to their use as spice possess a variety of Pharmacological actions.

REFERENCES

1. Gilani AU, Jabeen Q, Khan MA. A review of medicinal uses and pharmacological activities of Nigella sativa. Pak J Biol Sci. 2004;7(4):441-51.
2. SahihMuslim ; Book 26: Kitab As-Salam, Hadith Number 5489.
3. Padhye S, Banerjee S, Ahmad A, Mohammad R, Sarkar FH. From here to eternity-the secret of Pharaohs: Therapeutic potential of black cumin seeds and beyond. Cancer therapy. 2008;6(b):495.
4. Sharma NK, Ahirwar D, Jhade D, Gupta S. Medicinal and phamacological potential of nigella sativa: a review. Ethnobotanical Leaflets. 2009;2009(7):11.
5. Dwivedi SN, Dwivedi S, Patel PC. Medicinal plants used by the tribal and rural people of Satna District, Madhya Pradesh for the treatment of gastrointestinal diseases and disorders.
6. Aggarwal BB, Kunnumakkara AB, Harikumar KB, Tharakan ST, Sung B, Anand P. Potential of spice-derived phytochemicals for cancer prevention. Plantamedica. 2008 Oct;74(13):1560-9.
7. Plant profile of Nigella sativa.:http://plants.usda.gov/java/profile?symbol=NISA2
8. Dwivedi SN. Ethnobotanical studies and conservational strategies of wild and natural resources of Rewa district of Madhya Pradesh. Journal of economic and taxonomic botany. 2003;27(1):233-44.
9. Hajhashemi V, Ghannadi A, Jafarabadi H. Black cumin seed essential oil, as a potent analgesic and antiinflammatory drug. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2004 Mar;18(3):195-9.
10. Abdel-Fattah AF, Matsumoto K, Watanabe H. Antinociceptive effects of Nigella sativa oil and its major component, thymoquinone, in mice. European journal of pharmacology. 2000 Jul 14;400(1):89-97.
11. Al-Naggar TB, Gomez-Serranillos MP, Carretero ME, Villar AM. Neuropharmacological activity of Nigella sativa L. extracts. Journal of ethnopharmacology. 2003 Sep 1;88(1):63-8.
12. Al-Ghamdi MS. The anti-inflammatory, analgesic and antipyretic activity of Nigella sativa. Journal of ethnopharmacology. 2001 Jun 1;76(1):45-8.
13. Tanko Y, Mohammad A, Okasha MA, Shuaibu A, Magaji MG, Yaro AH. Analgesic and anti-inflammatory activities of ethanol seed extract of Nigella sativa (black cumin) in mice and rats. Euro J Sci Res 2007; 18:277-81.

14. Mehta BK, Pandit V, Gupta M. New principles from seeds of Nigella sativa. Natural product research. 2009 Jan 20;23(2):138-48.
15. Perveen R. Therapeutic effects of black cumin (Nigella sativa). A systematic review. Progress in Nutrition. 2019 May 6;21(1-S):40-9.
16. Hosseinzadeh H, Parvardeh S, Nassiri-Asl M, Mansouri MT. Intracerebroventricular administration of thymoquinone, the major constituent of Nigella sativa seeds, suppresses epileptic seizures in rats. Medical Science Monitor. 2005 Apr 1;11(4):BR106-10.
17. Perveen T, Haider S, Kanwal S, Haleem DJ. Repeated administration of Nigella sativa decreases 5-HT turnover and produces anxiolytic effects in rats. Pakistan Journal of Pharmaceutical Sciences. 2009 Apr 1;22(2).
18. Al-Majed AA, Al-Omar FA, Nagi MN. Neuroprotective effects of thymoquinone against transient forebrain ischemia in the rat hippocampus. European journal of pharmacology. 2006 Aug 14;543(1-3):40-7.
19. Dehkordi FR, Kamkhah AF. Antihypertensive effect of Nigella sativa seed extract in patients with mild hypertension. Fundamental & clinical pharmacology. 2008 Aug;22(4):447-52.
20. Yar T, El-Hariri M, El-Bahai MN, Bamosa AO. Effects of Nigella sativa supplementation for one month on cardiac reserve in rats. Indian J PhysiolPharmacol. 2008;52(2):141-8.
21. Zaoui A, Cherrah Y, Alaoui K, Mahassine N, Amarouch H, Hassar M. Effects of Nigella sativa fixed oil on blood homeostasis in rat. Journal of Ethnopharmacology. 2002 Feb 1;79(1):23-6.
22. Bamosa A, Ali BA, Al-Hawsawi ZA. The effect of thymoquinone on blood lipids in rats. Indian journal of physiology and pharmacology. 2002 Apr;46(2):195-201.
23. Fararh KM, Atoji Y, Shimizu Y, Takewaki T. Isulinotropic properties of Nigella sativa oil in Streptozotocin plus Nicotinamide diabetic hamster. Research in veterinary science. 2002 Dec 1;73(3):279-82.
24. El-Mahmoudy A, Shimizu Y, Shiina T, Matsuyama H, El-Sayed M, Takewaki T. Successful abrogation by thymoquinone against induction of diabetes mellitus with streptozotocin via nitric oxide inhibitory mechanism. International immunopharmacology. 2005 Jan 1;5(1):195-207.
25. Arayne MS, Sultana N, Mirza AZ, Zuberi MH, Siddiqui FA. In vitro hypoglycemic activity of methanolic extract of some indigenous plants. Pak J Pharm Sci. 2007 Oct 1;20(4):268-73.
26. Ural ÜM, Tekin YB, Şehitoğlu İ, Kalkan Y, Cüre MC. Biochemical, histopathological and immunohistochemical evaluation of the protective and therapeutic effects of thymoquinone against ischemia and ischemia/reperfusion injury in the rat ovary. Gynecologic and obstetric investigation. 2016;81(1):47-53
27. Wienkötter N, Höpner D, Schütte U, Bauer K, Begrow F, El-Dakhakhny M, Verspohl EJ. The effect of nigellone and thymoquinone on inhibiting trachea contraction and mucociliary clearance. Plantamedica. 2008 Feb;74(02):105-8.
28. El Gazzar MA, El Mezayen R, Marecki JC, Nicolls MR, Canastar A, Dreskin SC. Anti-inflammatory effect of thymoquinone in a mouse model of allergic lung inflammation. IntImmunopharmacol 2006; 6:1135-42.
29. El-Abhar HS, Abdallah DM, Saleh S. Gastroprotective activity of Nigella sativa oil and its constituent, thymoquinone, against gastric mucosal injury induced by ischaemia/reperfusion in rats. Journal of ethnopharmacology. 2003 Feb 1;84(2-3):251-8.
30. Kanter M, Demir H, Karakaya C, Ozbek H. Gastroprotective activity of Nigella sativa L oil and its constituent, thymoquinone against acute alcohol-induced gastric mucosal injury in rats. World Journal of Gastroenterology: WJG. 2005 Nov 14;11(42):6662.
31. Rajkapoor B, Anandan R, Jayakar B. Anti-ulcer effect of Nigella sativa Linn. against gastric ulcers in rats. Current Science. 2002 Jan 25:177-9.
32. Juhás S, Cikos S, Czikková S, Veselá J, Il kova G, Hájek T, Domaracká K, Domaracky M, Bujnáková D, Rehák P, Koppel J. Effects of borneol and thymoquinone on TNBS-induced colitis in mice. FOLIA BIOLOGICA-PRAHA-. 2008 Jan 1;54(1):1.
33. Khither H, Sobhi W, Mosbah A, Benboubetra M. Prophylactic and Curative Effects of Thymoquinone against CCL4-Induced Hepatotoxicity in Rats. European

Journal of Medicinal Plants. 2018 Jan 11:1-8.

34. Laskar AA. Hepatoprotective Action of Thymoquinone. InMolecular and Therapeutic actions of Thymoquinone 2018 (pp. 65-74). Springer, Singapore.
35. Yildiz F, Coban S, Terzi A, Ates M, Aksoy N, Cakir H, Ocak AR, Bitiren M. Nigella sativa relieves the deleterious effects of ischemia reperfusion injury on liver. World journal of gastroenterology: WJG. 2008 Sep 7;14(33):5204.
36. Meral I, Donmez N, Baydas B, Belge F, Kanter M. Effect of Nigella sativa L. on heart rate and some haematological values of alloxan-induced diabetic rabbits. Scandinavian Journal of Laboratory Animal Sciences. 2004;31(1):49-53.
37. Zaher KS, Ahmed WM, Zerizer SN. Observations on the biological effects of black cumin seed (Nigella sativa) and green tea (Camellia sinensis). Global Veterinaria. 2008;2(4):198-204.
38. Salem ML. Immunomodulatory and therapeutic properties of the Nigella sativa L. seed. International immunopharmacology. 2005 Dec 1;5(13-14):1749-70.
39. Gholamnezhad Z, Rafatpanah H, Sadeghnia HR, Boskabady MH. Immunomodulatory and cytotoxic effects of Nigella sativa and thymoquinone on rat splenocytes. Food and Chemical Toxicology. 2015 Dec 1;86:72-80
40. Salah AS, El-Tarabany MS, Ali MA. Impact of dietary supplementation with a synbiotic, organic acids or their combination on growth performance, carcass traits, economic efficiency, jejunum histomorphometry and some blood indices of broiler chickens. Animal Production Science. 2019 Jun 15;59(7):1318-26.
41. Nazrul Islam SK, Begum P, Ahsan T, Huque S, Ahsan M. Immunosuppressive and cytotoxic properties of Nigella sativa. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2004 May;18(5):395-8.
42. Shoieb AM, Elgayyar M, Dudrick PS, Bell JL, Tithof PK. In vitro inhibition of growth and induction of apoptosis in cancer cell lines by thymoquinone. International journal of oncology. 2003 Jan 1;22(1):107-13.
43. Gali-Muhtasib H, Diab-Assaf M, Boltze C, Al-Hmaira J, Hartig R, Roessner A, Schneider-Stock R. Thymoquinone extracted from black seed triggers apoptotic cell death in human colorectal cancer cells via a p53-dependent mechanism. International journal of oncology. 2004 Oct 1;25(4):857-66.
44. Roepke M, Diestel A, Bajbouj K, Walluscheck D, Schonfeld P, Roessner A, Schneider-Stock R, Gali-Muhtasib H. Lack of p53 augments thymoquinone-induced apoptosis and caspase activation in human osteosarcoma cells. Cancer biology & therapy. 2007 Feb 1;6(2):160-9.
45. Gali-Muhtasib H, Ocker M, Kuester D, Krueger S, El-Hajj Z, Diestel A, Evert M, El-Najjar N, Peters B, Jurjus A, Roessner A. Thymoquinone reduces mouse colon tumor cell invasion and inhibits tumor growth in murine colon cancer models. Journal of cellular and molecular medicine. 2008 Jan;12(1):330-42.
46. Richards LR, Jones P, Hughes J, Benghuzzi H, Tucci M. The physiological effect of conventional treatment with epigallocatechin-3-gallate, thymoquinone, and tannic acid on the LNCaP cell line. Biomedical sciences instrumentation. 2006;42:357-62.
47. Martin TM, Benghuzzi H, Tucci M. The effect of conventional and sustained delivery of thymoquinone and levodopa on SH-SY5Y human neuroblastoma cells. Biomedical sciences instrumentation. 2006;42:332-7.
48. Hadjzadeh MAR, Khoei A, Hadjzadeh Z, Parizady M. Ethanolic extract of Nigella sativa L. seeds on ethylene glycol-induced kidney calculi in rats. Urol J 2007; 4:86-90.
49. Mohammad MA, Mohamad MM, Dradka H. Effects of black seeds (Nigella sativa) on spermatogenesis and fertility of male albino rats. Research Journal of Medicine and Medical Sciences. 2009;4(2):386-90.
50. Hosseinzadeh H, Bazzaz BSF, Haghi MM. Antibacterial activity of total extracts and essential oil of Nigella sativa L. seeds in mice. Pharmacolgyonline 2007; 2:429-35.
51. Halawani E. Antibacterial activity of thymoquinone and thymohydroquinone of Nigella sativa L. and their interaction with some antibiotics. Advances in Biological Research. 2009;3(5-6):148-52.

52. Salem ML, Hossain MS. Protective effect of black seed oil from Nigella sativa against murine cytomegalovirus infection. International journal of immunopharmacology. 2000 Sep 1;22(9):729-40.
53. AUREUS NS. Antibacterial and antifungal effects of Nigella sativa extracts against S. aureus, P. aeroginosa and C. albicans. Pak J Med Sci January-March. 2005;21(1):47-52.
54. Ekanem JT, Yusuf OK. Some biochemical and haematological effects of black seed (Nigella sativa) oil on Trypanosomabrucei-infected rats. African journal of Biotechnology. 2008;7(2).
55. El-Dakhakhny M, Madi NJ, Lembert N, Ammon HP. Nigella sativa oil, nigellone and derived thymoquinone inhibit synthesis of 5-lipoxygenase products in polymorphonuclear leukocytes from rats. Journal of ethnopharmacology. 2002 Jul 1;81(2):161-4.
56. Badary OA, Abdel-Naim AB, Abdel-Wahab MH, Hamada FM. The influence of thymoquinone on doxorubicin-induced hyperlipidemic nephropathy in rats. Toxicology. 2000 Mar 7;143(3):219-26.
57. Tekeoglu I, Dogan A, Ediz L, Budancamanak M, Demirel A. Effects of thymoquinone (volatile oil of black cumin) on rheumatoid arthritis in rat models. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2007 Sep;21(9):895-7.

Case Report

SPONTANEOUS BILATERAL TUBAL ECTOPIC PREGNANCY

Ambreen Mumtaz and Uzma Siddique

Abstract:
Bilateral spontaneous tubal pregnancy is the rarest form of ectopic pregnancy. Bilateral tubal pregnancy in the absence of proceeding ovulation induction is rare, with an incidence of 1 in 725 to 1 in 1580 ectopic pregnancies. Preoperative diagnosis is difficult because ultrasound has its limitations. They are usually diagnosed at the time of surgery. We report a case of spontaneous bilateral tubal pregnancy. A 35 years old patient with parity 3 and 1 abortion was admitted with the complaint of pain in lower abdomen with vaginal bleeding for 1 month. Laparotomy was done for the diagnosis of single ectopic pregnancy but diagnosis of bilateral tubal pregnancy was made intraoperatively. Bilateral salpingectomy was performed without complication and histopathology report confirmed the diagnosis. This highlights the importance of closely examining both tubes at the time of surgery in order to prevent maternal morbidity and mortality.

Key Words: Ectopic pregnancy, Tubal Pregnancy, Assisted Reproductive Technique,

INTRODUCTION:

Ectopic pregnancy constitutes one of the leading causes of pregnancy-related maternal deaths. According to WHO 2007, 5% of maternal mortality in the developed countries is due to ectopic pregnancy.[1,2]

Exact incidence remains unknown as the diagnosis is often missed when the ectopic pregnancy resolves spontaneously at an early stage. Recently, the problem of ectopic pregnancy has been magnified due to advanced maternal age, pelvic inflammatory disease (PID), tubal surgery, intrauterine device, infertility and assisted reproductive technique (ART).

Spontaneous bilateral tubal pregnancy is a rare disease that occurs in 1 per 200,000 pregnancies.[1] The incidence of bilateral tubal pregnancy has been reported to be increasing as a result of increased use of induction ovulations. However, bilateral tubal pregnancy in the absence of preceding ovulation induction is a rare condition with an estimated incidence of 1 in 725 to 1 in 1580 ectopic pregnancies.[2]

Department of Obstetrics and Gynaecology, Akhtar Saeed Trust Hospital, Lahore

The rarest from of ectopic pregnancy is bilateral tubal pregnancy which occurs spontaneously.[2]

Most patients with bilateral tubal pregnancies have similar risk factors to those with unilateral ectopic pregnancy.[3,4]

CASE REPORT:

The patient was 35-year-old P3, with previous vaginal deliveries and history of miscarriage 4 months back followed by evacuation by the dai. After that, she had 2 normal menstrual cycles and in the third month, she developed pain in lower abdomen and continuous P/V bleeding for 1 month. There was no history of contraception, any abdominopelvic surgery or use of ovulation induction. However, there was history of vaginal discharge off and on for many years.

The patient was haemodynamically stable. There was tenderness in lower abdomen. On pelvic examination, uterus was bulky, tenderness was present on mobility of cervix and fullness noted in the posterior and left fornix. Bleeding was mild. Haematological evaluation showed Hemoglobin = 10gm/dl ,Hematocrit = 30% ,WBC count =

6400/mm^3 and Beta HCG was 5700iu/l. Ultrasound report revealed a left adnexal mass measuring 5.3x5.1 cm and uterine cavity was empty, with moderate amount of fluid in the pelvis. Right adnexa was unremarkable and measured 2.4 x 1.8cm. Exploratory laparotomy was performed which revealed haemoperitoneum. Left tube was swollen, bleeding and partially ruptured with 500 cc clots removed from cul-de-sac. When right tube was examined for its status, then right intact ectopic pregnancy was diagnosed (refer to diagram D1, D2). Consent for tubal ligation was taken already so bilateral salpingectomy was done. Postoperative course was uneventful. Pathology report confirmed the diagnosis of bilateral tubal ectopic pregnancy.

Picture=D-1

Picture=D-2

DISCUSSION:

Spontaneous bilateral tubal pregnancy is a rare entity[5] and more than 200 case reports of bilateral tubal pregnancy have been reported in the literature, and most cases occurred after using assisted reproductive techniques.[6]

We have reported a case of one ruptured and one intact ectopic pregnancy. Ultrasonography in our case diagnosed only a left ectopic pregnancy and right intact tubal pregnancy was missed on ultrasound. It was diagnosed on laparotomy when other tube was checked for its status as mentioned in other cases in the literature.[7]

Ultrasonography and laparoscopy both have limitations so preoperative diagnosis of bilateral ectopic remains a challenge. Most patients with bilateral ectopic have similar symptoms and risk factors to those of unilateral ectopic pregnancy. Comprehensive clinical guidelines for treatment of ectopic pregnancy have been published by Royal College of Obstetrics and Gynaecology, because of its rarity bilateral ectopic pregnancy is not covered but principles of treatment can still be applied and it ranges from bilateral salpingectomy to conservative approaches such as salpingostomy and salpingotomy.[2] Since the diagnosis of bilateral tubal pregnancy is usually made at time of surgery, there are no case reports of successful primary medical treatment with methotrexate.

In our case, we did the salpingectomy for left ruptured ectopic then other tube was checked for its status and other intact right ectopic pregnancy was diagnosed. As consent for tubal ligation was already taken so bilateral salpingectomy was done and specimen sent for histopathology.

Chances of recurrent ectopic pregnancy in the future are increased after an ectopic pregnancy. The necessity of carefully examining both adnexa, as postulated by Sherman cannot be overemphasized.[8] Cases of ectopic pregnancy have been reported

after bilateral salpingectomy. This highlights the need of high suspicion in case when tubal ligation and bilateral salpingectomy patient presents with amenorrhea.

REFERENCES:

1. Ghomian N, Lotfalizadeh M. Spontaneous unruptured bilateral tubal pregnancy: a case report. Iranian journal of medical sciences. 2015 Nov;40(6):537.
2. Andrews J, Farrell S. Spontaneous bilateral tubal pregnancies: a case report. Journal of Obstetrics and Gynaecology Canada. 2008 Jan 1;30(1):51-4.
3. Bouyer J, Coste J, Shojaei T, Pouly JL, Fernandez H, Gerbaud L, Job-Spira N. Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France. American Journal of Epidemiology. 2003 Feb 1;157(3):185-94.
4. Karaer A, Avsar FA, Batioglu S. Risk factors for ectopic pregnancy: A case-control study. Australian and New Zealand journal of obstetrics and gynaecology. 2006 Dec;46(6):521-7.
5. Clark SL, Belfort MA, Dildy GA, Herbst MA, Meyers JA, Hankins GD. Maternal death in the 21st century: causes, prevention, and relationship to cesarean delivery. American journal of obstetrics and gynecology. 2008 Jul 1;199(1):36-e1.
6. Lang CT, King JC. Maternal mortality in the United States. Best Practice and Research Clinical Obstetrics and Gynaecology. 2008 Jun 1;22(3):517-31.
7. Othman M, Karali S, Badawi K, Mossa H. Bilateral ectopic pregnancy: case report.
8. Katler Q, Pflugner L, Martinez A. Management of Bilateral Ectopic Pregnancies after Ovulation Induction Using Unilateral Salpingectomy and Methotrexate for the Remaining Ectopic with Subsequent Intrauterine Pregnancy. Case Reports in Obstetrics and Gynecology. 2018;1(1):4