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Editorial **Open Access**

Emotional Intelligence: A Valued Workplace Competency

Kiran Fatima, Ijaz Lateef

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Some employees may exhibit emotional symptoms such as work pressure, agitation, anxiety, depression and irritability .[1]These symptoms are related to the various dimensions of the emotional intelligence (EI). These emotions have emotional impact over employee's performance positively or negatively. It can lead to poor performance, less work determination or low morale. Emotional Intelligence (EI) is the capability to recognize, control and manage owns emotions and to recognize and manage the emotions of the other person. Hence, emotionally intelligent individuals can recognize their feelings, interpret and regulate their emotions, distinguish how these emotions would have an impact on others and manage emotions of others.

Some individuals have a high emotional quotient and these skills develop with the influence of attachment with any senior in family. Moreover; these skills can be learnt and acquired by continuous professional development and adaptability mechanism.[1] Constant practicing of behaviours makes the person proficient. Thereby the brain can acclimatize these behaviours and take the place of less productive and less helpful behaviours.

There are various skills required to manage the emotions such as self-regulation, discipline, empathy, self-awareness, self-perception, intrinsic motivation and social skills. Worldwide; these skills are top most skills for recruiting any employee from human resource department of most organizations.[2] It is well known that emotions at workplace have effect on interpersonal relationship, collaboration; management, problem solving and communication skills and eventually creating happier work environment. Hence Emotional Intelligence at work place has the direct impact over employee's performance, intrinsic motivation and ultimately over the success of organization.[3]

Some recommend that emotions should be left at door place while commencing work. But realistically human beings are full of emotions. Inability to understand and deal with human emotions is an ill-fated drift. It can negatively affect employee's performance from lower to top management. To address this many organizations have hired psychologists and provide mental health coverage to their workforce. This ensures healthier workplace environment by providing useful training to augment strong workplace relationships. Employees would have determination and the office is full of emotionally intelligent workforce where everyone respects and gets along with each other. Eventually employee enjoys the working relations. In the long run the organization has realistic paybacks, success and would be able to provide quality customer care services. According to the study conducted in Sialkot Pakistan; EI has the effect on sales performance and on customer's relationship. This study revealed significantly positive relationship between three competencies of EI and sales performance of employees such as empathy (30%), self-management (27.5%) and social management (24.2%).[4]

Yet various organizations do not value skills required for managing emotional intelligence at workplace and resulting in poor reputation and organizational failure.[3]

The leaders of peak growing and successful companies have higher emotional intelligence. [4] The emotionally intelligent managers are outstanding leaders and outclassed performed yearly revenue by 20%.[4] Goleman suggested that emotional intelligence is the main theory of performance.[6] He proposed an association between leadership and emotional intelligence.[7] The literature suggests a significant and positive relationship between empowering leadership, emotional intelligence, work engagement and psychosocial empowerment.[8] The difference between the stratum of emotional intelligence in men and women is reported but on the contrary this level can be enhanced as per need and growth.[7] Therefore, emotional intelligence has the potential towards contributing outstanding performance at workplace and results in workplace success.

In healthcare setting, physicians with high levels of emotional intelligence are better able to understand and manage patients. They can effectively counsel the patients with health and psychosocial issues. Managers are more proficient to integrate various skills to provide quality healthcare services and are successful at workplace[9] and are regarded by top management and subordinates as compared to those managers having devoid of EI. Furthermore, EI nurses exhibited less work

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stress and are cross cultured.[10] EI training during COVID-19 nurtured the wellbeing and work engagement of nurses according to the study conducted in Pakistan regarding cross cultural practices.[10] Thus, EI is mandatory and valued competencies in healthcare setting and is more valued skill at workplace.

Emotional guidelines at workplace can be learnt from informal, formal socialization, punishment and reward. It has been stressed that at workplace career development, performance and success is depend upon the utilizing the skills of emotional intelligence. Human resource department has the special focus to develop these capabilities through career motivation sessions in some organizations. Consequently this knowledge is swayed by cultural and social pressures, environmental perspective such as organizational climate and biological forces. But on the other hand person with high emotional intelligence can balance these forces at workplace and moving towards achieving the targets and mission by healthier working relations.

In some workplace settings, employees are empowered by providing supportive working environment and greater autonomy. This is known as empowering leaders. [11, 12] In educational setting; EI teachers are performing well in their career. [13] Trickledown effect of empowering leaders results in work success.[13] It is recommended that organization has to restructure their workplace culture and realize the true potential of employees. EI skills can be integrated in undergraduate and post graduate curriculum of medical education as to bring workplace success in due course of time.

Authors Contribution:
Kiran Fatima: Idea Conception, write up
Ijaz Lateef: Proof Reading

REFERENCES:

1. Kafetsios K., Attachment and emotional intelligence abilities across the life course, Personality and Individ. Differences 37: 2004; 129–145
2. Zhang, S., Ke, X., Wang, X-H.F. and Liu, J."Empowering leadership and employee creativity: a dual-mechanism perspective", Journal of Occupational and Organizational Psychology. 2018; 91(4); 896-917.
3. Iguodala-Cole HI. The importance of emotional intelligence skills in the work place: A sociological perspective. HUMANUS DISCOURSE. 2021;1(3)1;1-5
4. Ali M. Impact of emotional intelligence competencies on sales performance of employees in surgical trading firms in Pakistan; 2018 (Doctoral dissertation, Dublin Business School).
5. Goleman, D. Emotional intelligence: perspectives on a theory of performance. New York: Bantam Books. (2001).
6. Goleman, D. Working with emotional intelligence .New York: Bantam Books. (1998).
7. Salovey, P. and Mayer, J.D. (1990), "Emotional intelligence", Imagination, Cognition and Personality; 9(1)1; 185-211
8. Alotaibi SM, Amin M, Winterton J. Does emotional intelligence and empowering leadership affect psychological empowerment and work engagement?. Leadership & Organization Development Journal. 2020; 971-991.
9. K. Adams, J. Cimino, R. Arnold, W. Anderson, Why should I talk about emotion? Communication patterns assicated with physician discussion of patient expressions of negative emotion in hospital admission encounters, Patient Educ. Couns. 2012; 89 (4);44–50.
10. Alam F. COVID-19 and well-being among nurses: The Role of Cross-Cultural Practices and Emotional Intelligence in the tertiary hospitals of Pakistan J NursPatient Care. of. 2021;9:2.
11. Kim, M., Beehr, T.A. and Prewett, M.S."Employee responses to empowering leadership: a meta-analysis", Journal of Leadership and Organizational Studies. 2018; 25(3); 257-276
12. Kim, M. and Beehr, T.A. (2018), "Organization-based self-esteem and meaningful work mediate effects of empowering leadership on employee behaviours' and well-being", Journal of Leadership and Organizational Studies. 2018; 25 (4); 385-398
13. Byun, G., Lee, S., Karau, S.J. and Dai, Y. "The trickle-down effect of empowering leadership: a boundary condition of performance pressure", Leadership and Organization Development Journal. 2020; 41(3);399-414
14. Zaid S, Hussain K, Ullah MZ. Impact Of Emotional Intelligence On Teachers'perceived Performance: Empirical Evidence From Higher Education Sector Of Pakistan. Pakistan Journal of Educational Research. 2021 Dec 31;4(4).
15. Cherry MG, Fletcher I, Berridge D, O'Sullivan H. Do doctors' attachment styles and emotional intelligence influence patients' emotional expressions in primary care consultations? An exploratory study using multilevel analysis. Patient education and counselling. 2018;101(4):659-64.

Original Article **Open Access**

Determining the Effect of Intrathecal Dexmedetomidine on Postoperative Pain Relief after Cesarean Section

Ayesha Shahid, Huda Shafqat, Salman Maqbool, Ahsan Ali, Rehana Feroze

ABSTRACT:

Objective: To analyze efficacy of intrathecal Dexmedetomidine as adjunct to hyperbaric Bupivacaine in terms of post-operative analgesia after caesarean section.

Study Design & Setting: This randomized controlled trial was conducted at Department of Anesthesia, Rawal Institute of Health Sciences, Islamabad from20th, October 2018 to 20thApril 2019 after taking Ethical board approval from the Institute. (letter no RIHS-REC/030/18, dated, 18th October 2018).

Methodology: Total n=120 patients having ASA status I, II undergoing elective cesarean section were randomly divided into 2groups (60 each) by lottery method. Group-A, was given hyperbaricBupivacaine (0.5%) 12mg alone and group-B, was given hyperbaricBupivacaine (0.5%) 12mg along with injection Dexmedetomidine 4ug in intrathecal space respectively. Patients were followed in postoperative period for onset of pain and requirement for rescue analgesia in first 6 hours.

Results: There was statistically significant difference in mean onset of postoperative pain among both the groups-A and B (178.18 ± 12.51 versus 364.07± 35.58min respectively with p value 0.000), as well as, postoperative analgesic requirement, in first 6 hours, 39 (65.0 %) versus 31 (51.7 %) with p-value 0.000 respectively. However, on stratification, considering effect modifiers, like age (20-30 years and 30-40 year and previous history of cesarean section), there was statistically significant difference in mean onset of pain in both groups, but no significant difference was found regarding rescue analgesic requirement in both groups.

Conclusion: Intrathecal Dexmedetomidine along with hyperbaric Bupivacaine was better than hyperbaric Bupivacaine alone in controlling postoperative pain in caesarean section.

Keywords: Cesarean section, Dexmedetomidine, Hyperbaric bupivacaine, Intrathecal space.

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INTRODUCTION:

Caesarean sections are usually performed under neuraxial anesthesia. This practice was well established since beginning of 20th century. Its prevalence has been reported to be 32.5 % in African countries with 68.2 % cases performed under regional anesthesia.[1] As far as patient safety is concerned neuraxial anesthesia is a safe procedure as compared to general anesthesia.[2] It provides pain relief by blocking nociceptive transmission from peripheral to central nervous system. Since local anesthetics have got short half-life so they didn't provide long term pain relief in postoperative period. Increasing the dose of local anesthetic to achieve prolong analgesia in post operative period can result in systemic as well as potential neurotoxicity.[3] The analgesic effects of local anesthetic drug used in subarachnoid block can be increased by adding adjunct such as clonidine, opioids, ketamine, magnesium, dexamethasone, midazolam and tramadol. They not only enhance quality of block but also helps in keeping stable hemodynamics intraoperatively.[4] Pain after cesarean section is one of the most common postoperative problems, hence adequate postoperative analgesia is required for postpartum women. It not only increases patient satisfaction but also leads to earlier mobilization, decrease risk of thromboembolism, reduce hospital stay as well as hospital costs.[5]It also facilitate initiation of breast-feeding as hormonal changes and stress response due to pain may interfere with lactation. All these factors help to improve patient satisfaction in postpartum period.[6]

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Postoperative pain is usually treated with opioids that have their own side effects.[7] The side effects include pruritus, nausea, vomiting and respiratory depression.[8] Dexmedetomidine is one of the most common drugs that is being used as adjunct to bupivacaine in subarachnoid space. Dexmedetomidine has opioids sparing effect, therefore can be safely used as an adjunct for post operative pain relief.[5] It inhibits activation of spinal microglia and astrocytes to produce its antinociception effect. It also inhibits release of nociceptive substances that are triggered by painful stimuli.[3] In addition to its analgesic potency, it has got sedative, anxiolytic as well as sympatholytic properties.[9] Studies have shown that Dexmedetomidine when used alone is not a good analgesic , however when used as an adjunct in subarachnoid block, it improves onset of sensory and motor block, hemodynamic stability and prolongs the duration of analgesia.[10]In addition to its use as adjunct in subarachnoid space ,studies have shown that it has got synergistic effect with duration of subarachnoid block when given through intravenous route.[3]As Dexmedetomidine has recently been introduced contextually, thus existed data is limited at national level to evaluate the postoperative analgesic effect of intrathecal dexmedetomidine as an adjunct along with hyperbaric bupivacaine. Thus, the rationale of this study was to find better management for post-operative analgesia in caesarean section. This study was aimed to analyze the effect of intrathecal dexmedetomidine with hyperbaric bupivacaine on post operative analgesia in caesarean section.

METHODODOLOGY:

This study was conducted at Department of Anesthesia and critical care Rawal Institute of Health Sciences Islamabad from 20th, October 2018 to 20th April,2019 after taking Ethical board approval(letter no RIHS-REC/030/18, dated, 18th October 2018). Nonprobability consecutive sampling technique was well thought for this pilot study. Total n=120 patients with age 20-40 years, having ASA[11] status category I and II, planned for elective c- section were enrolled in this study. Patients with severe hypovolemia, coagulopathy, history of spinal stenosis, heart block and taking clonidine were excluded from study. Using WHO sample size calculator with following assumptions (confidence level=95%, Power of test=80%, population mean onset of pain in group 1=220.75mins, population mean onset of pain in group 2=1042.5mins [12]) sample size was calculated as 120 (60 cases placed into each group A and B by lottery method). All the patients gave informed written consent to participate in this trail. After standard 8 hours fasting, all patients were premedicated with injection metoclopramide 10 mg and inj. Dexamethasone 4mg intravenously. In the operation theatre, standard monitoring (ECG, BP, HR, pulse oximetry) was done and recorded. Group-A, patients were given inj. hyperbaric Bupivacaine (0.5%) 12mg and group B were given inj. hyperbaric Bupivacaine (0.5%) 12mg along with injection Dexmedetomidine 4ug in intrathecal space respectively. After completion of surgery, patients were transferred to recovery room and observed there for half hour. Patients were followed in postoperative period for onset of pain and analgesic requirement in first 6 hours. All findings were recorded on the specially designed proforma. Confidentiality of the record was maintained. SPSS version 21 was used.

RESULTS:

Mean age of patients was 32.12± 8.48 years in group A and 31.83 ± 8.84 years in group B respectively. There was statistically significant difference (P-value 0.000) in time for onset of pain in postoperative period in both groups as shown in table 1. Postoperative analgesic requirement was compared in terms of frequency in both groups. There was statistically significant difference (P- value 0.000) among both groups with 39 (65.0%) patients in group A, as compared to 31 (51.7%) patients in group-B, who demanded analgesia in first 6 hours postoperative period as shown in (table 1).

Effect modifier like age stratification was assessed by dividing patients in two age group (20-30yrs) and 30-40 years (as shown in table-2). There was statistically significant difference in time for onset of pain in groups-A and B, however when frequency of patients who needed rescue analgesia in first 6 hours was compared among groups-A and B, no significant difference was found, considering the patients in two age groups.

Similarly effect modifier like previous history of cesarean section stratification was done (as shown in table-3) and results were compared in both groups-A and B. There was statistically significant difference in time for onset of pain in groups-A and B, however when frequency of patients who needed rescue analgesia in first 6 hours was compared in groups A and B, there was no significant difference.

DISCUSSION:

Major limitation of sub-arachnoid block is relatively short duration of block and lesser postoperative analgesia.[13] The commonly used local anesthetic is Bupivacaine that has long duration of action however in terms of post-operative analgesia its duration is short.[14]So various adjuvants have been used intrathecally along with Bupivacaine. The aim is to enhance quality of intraoperative as well as postoperative analgesia.[15] The most commonly used intrathecal adjuvants are opioids.[16]Their side effects includes postoperative nausea and vomiting,pruritus, difficulty to void and delayed respiratory depression, so studies have been done to use

Table-1: Comparison of Onset of Pain (Min) and analgesia required in first 6 hours (both groups). (n=120)

	Group A	Group B	P-value
Onset of Pain (Min)	178.18 ±12.51	364.07 ±35.58	0.000
Postoperative Analgesic Requirement (Frequency)	39(65.0%)	31(51.7%)	0.000

Table-2: Effect modifiers like Age stratification with comparison of Onset of Postoperative pain & Postoperative Analgesic requirement in first 6 hours among both the groups. (n=120)

Age Group		GROUP A	GROUP B	p-value
20-30yrs	Mean Onset of postoperative pain (in minutes)	175.88 ± 10.55	359.55 ± 60.78	0.000
	Postoperative analgesic requirement (frequency)	11(68.8%)	7(35.0%)	0.044
30-40 years	Mean Onset of postoperative pain (in minutes)	180.32 ± 10.90	369.44 ± 11.96	0.000
	Postoperative analgesic requirement (frequency)	28(63.6%)	24(60.0%)	0.453

Table-3: Effect modifiers like previous history of cesarean section stratification with comparison of Onset of Postoperative pain & Postoperative Analgesic requirement in first 6 hours in both Groups. (n=120)

Effect modifier	Parameter	Group A	Group B	p- value
No history of previous cesarean section	Mean Onset of postoperative pain (minutes)	178.38 ± 11.92	364.25 ± 36.05	0.000
	postoperative analgesic requirement(frequency)	20(69.0%)	12(42.9%)	0.047
History of previous cesarean section	Mean Onset of postoperative pain (minutes)	178.00 ± 13.23	363.91 ± 35.73	0.000
	postoperative analgesic requirement (frequency)	19(61.3%)	19(59.4%)	1.000

non-opioid analgesics with lesser side effects in place of opioid analgesics.[17]The á$_2$-agonists when used as adjuvant in subarachnoid space have antinociceptive action both for somatic as well as for visceral pain. In addition to its analgesic effects, it also has sedative sympatholytic property, hence it not only stabilizes hemodynamics in intraoperative period but also reduces requirement of anesthetic agent for maintainance.[18]Therefore, these drugs have been commonly used as adjuvants to Bupivacaine in spinal anesthesia.[19]Among alpha-2 agonist, Dexmedetomidine and Clonidine are most used. Dexmedetomidine has ability to prolong postoperative analgesic effect of local anesthetics with minimal side effects.[20]Since Clonidine is partial agonist at alpha receptors, hence specificity of Dexmedetomidine is 7-8 times higher than Clonidine.[21] Being a lipophilic drug, dexmedetomidine rapidly gets absorbed into the CSF and binds to alpha 2 receptors of spinal cord and produce its analgesic effects. Irrespective of its route of administration, it has ability to prolong duration of sensory as well as motor blockade induced by local anesthetics.[22]

This study was performed in patients undergoing cesarean sections. Results of this study were comparable to another study done by Bi KH. et al[18] in patients undergoing cesarean section. Sixty patients were randomly divided in three groups. Patients undergoing cesarean section were given intrathecal bupivacaine alone or in combination with dexmedetomidine 3ug or 5ug. Results of this trial showed that addition of dexmedetomidine as adjunct to bupivacaine not only prolongs duration of sensory and motor block but also reduces requirement of analgesics in postoperative period as seen in our study. There was no significant difference regarding hemodynamics in three groups. Visual analog score for pain was also small in dexmedetomidine group. Reduced levels of cortisol and interleukin 6 in dexmedetomidine group supported the evidence that it also blunts stress response to surgery.[18]

Another study was done by Abdulkadir Y in patients undergoing hernia repair. He compared normal saline (group 1) ,2 ug (group 2) and 4 ug (group 3) of Dexmedetomidine used as an adjuvant to hyperbaric Bupivacaine in intrathecal space and compare the results. The mean time for onset of pain was 220.75±112.7 min in group 1 versus 371.5±223.5 min in group 2 and 1042.50±366.78 min in group 3. When compared, the time for first pain sensation in group 3 was significantly longer than in groups 1 and 2 with p value <0.001. So, the results of this study[12] were like our trial.

Ganesh M, et al;did a randomized prospective double-blind study to analyze effect of Clonidine and Dexmedetomidine on quality of subarachnoid block when used as an adjuvant to Bupivacaine. They compared onset of sensory and motor block as well as postoperative pain score in both groups. Onset of sensory block was low in both Clonidine and Dexmedetomidine group as compared to Bupivacaine alone however duration of motor block was highest in Dexmedetomidine group. Time for rescue analgesia was lowest in both Clonidine and Dexmedetomidine group and postoperative pain score was significantly low in both groups as compared to Bupivacaine alone group, so results of this study were comparable to our study as far as pain scoring and time for rescue analgesia was considered.[8]

Another study was carried out in patients undergoing infraumbilical surgeries. Group 1 was given intrathecal Bupivacaine alone while group 2 was given intrathecal Bupivacaine with Dexmedetomidine 5ug. Onset of sensory block (208.33±19.18 seconds in Group I versus 129.33±14.8 seconds in Group II with p value <0.001) as well as onset of motor block (320.33±29.81 minutes in group 1 versus 226.33±31.86 minutes in group 2 with p value <0.001)was significantly higher in Bupivacaine alone group as compared to Dexmedetomidine group.Total duration of sensory block(188±11.86 minutes in Group I versus 317.70±16.16

minutes in Group II with p value<0.001) as well as duration of motor block (166.5±12.11 minutes in Group I versus 286.33±15.15 minutes in group 11 with p value <0.001) was significantly low in Bupivacaine group as compared to Dexmedetomidine group. Duration of analgesia was 333.6±20.67 minutes in Dexmedetomidine group versus 193.67±7.06 minutes in Bupivacaine alone group.[23]So, these resultswere like our trial.

Literature review shows another trial done by KanaziGE, et al among patients undergoing prostate or bladder surgery under spinal anesthesia. Dexmedetomidine and Clonidine were used as an adjunct to Bupivacaine and their effect were analyzed in terms of duration of motor and sensory block, sedation score and hemodynamic variability. Time for onset of motor block was significantly reduced in Clonidine and Dexmedetomidine group as compared to Bupivacaine alone group. In contrast to onset of block, time for regression of sensory and motor block was significantly higher in these groups. However, there was no significant difference in sedation score in all three groups.[19]

Another comparative study was done in patients who were undergoing spinal saddle block. Intra-thecal hyperbaric Bupivacaine 5 mg(group A) was compared with hyperbaric Bupivacaine 5 mg with Dexmedetomidine 5 ug. Postoperative duration of analgesia was significantly prolonged in Dexmedetomidine group (group B, 501 ± 306 minutes versus group A, 284 ± 58 minutes) with less analgesic requirements in Dexmedetomidine group however, as compared to previous mentioned study done in infraumbilical procedures, there was no significant difference in peak sensory block as well as magnitude of motor block, and side effects in both groups.[24]

Another study was done in orthopedic patients undergoing lower limb surgeries. Dexmedetomidine 3 ug was compared with Dexmedetomidine 5 ug as adjuvant to hyperbaric Bupivacaine in intrathecal space. There was no difference in demographic profile, time interval to achieve sensory block, motor block, duration of surgery and intraoperative hemodynamics (p value 0.05). however, time for first rescue analgesia was significantly shorter in Dexmedetomidine 3 ug as compared to Dexmedetomidine 5 ug (206.47 min versus 271.33 min with p value <0.001).[25]

Further studies must be conducted at multiple setups at national level to emphasize adjuvant effect of intrathecal dexmedetomidine with hyperbaric bupivacaine on post-operative pain relief in caesarean section so that better management could be adopted in future.

Authors Contribution:
Ayesha: Concept & Design of Study, Drafting, Revisiting Critically, Data Analysis, Final Approval of version
Huda Shafqat: Concept & Design of Study, Drafting, Data Analysis
Salman Maqbool: Concept & Design of Study, Drafting, Revisiting Critically, Data Analysis, Final Approval of version
Ahsan Ali: Concept & Design of Study, Data Analysis
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REFERENCES:

1. Shitemaw T, Jemal B, Mamo T, Akalu L. Incidence and associated factors for hypotension after spinal anesthesia during cesarean section at Gandhi Memorial Hospital Addis Ababa, Ethiopia. PLoS One 2020;15(8):e0236755. doi.org/10.1371/journal.pone.0236755
2. Moore DC, Bridenbaugh LD. Spinal (Subarachnoid) Block: A Review of 11,574 Cases.JAMA 1966;195(11):907– 912. Doi:10.1001/jama.195.11.907
3. Wu HH, Wang HT, Jin JJ, Cui GB, Zhou KC, Chen Y, Chen GZ, Dong YL, Wang W. Does dexmedetomidine as a neuraxial adjuvant facilitate better anesthesia and analgesia? A systematic review and meta-analysis. PLoS One 2014 ;9(3):e93114. doi: 10.1371/journal.pone.0093114.
4. Zahid F, Tarar HM, Tariq M. Intrathecal tramadol as an adjuvant in subarachnoid block to prolong the duration of analgesia. PAFMJ 2017; 67(4): 534-39.
5. Ahmed F, Khandelwal M, Sharma A. A comparative study of the effect of clonidine, fentanyl, and the combination of both as adjuvant to intrathecal bupivacaine for postoperative analgesia in total abdominal hysterectomy. J Anaesthesiol Clin Pharmacol 2017;33(1):102-106. doi:10.4103/0970-9185.202194
6. Bhardwaj S, Devgan S, Sood D, Katyal S. Comparison of Local Wound Infiltration with Ropivacaine Alone or Ropivacaine Plus Dexmedetomidine for Postoperative Pain Relief after Lower Segment Cesarean Section. Anesth Essays Res 2017;11(4):940-945. doi: 10.4103/aer.AER_14_17
7. Nie Y, Tu W, Shen X et al. Dexmedetomidine added to sufentanil patient-controlled intravenous analgesia relieves the postoperative pain after cesarean delivery:A prospective randomised controlled multicenter study. Sci Rep 2018; 8: 9952.
8. Ganesh M, Krishnamurthy D. A comparative study of dexmedetomidine and clonidine as an adjunct to intrathecal bupivacaine in lower abdominal surgeries. Anesth Essays Res 2018; 12: 539-545. DOI: 10.4103/aer.AER_54_18
9. Lee S. Dexmedetomidine: present and future directions. Korean J Anesthesiol. 2019;72(4):323-330. doi:10.4097 /kja.19259
10. Javahertalab M, Susanabadi A, Modir H, Kamali A, Amani A, Almasi-Hashiani A. Comparing intravenous dexmedetomidine and clonidine in hemodynamic changes and block following spinal anesthesia with ropivacaine in lower limb orthopedic surgery: a randomized clinical trial. Med Gas Res 2020;10(1):1-7. doi:10.4103/2045-9912.279977
11. Morgan GE, Mikhail MS. Clinical Anesthesiology.6th Edition. McGraw Hill Education 2018; 18:523.

12. Yektas A, Belli E. The effects of 2ug and 4ug doses of dexmedetomidine in combination with intrathecal hyperbaric bupivaineon spinal anaesthesia and its postoperative analgesic characteristics. Pain Res Manay 2014; 19(2):75-81. doi: 10.1155/2014/956825.

13. Boublik J, Gupta R, Bhar S, Atchabahian A. Prilocaine spinal anesthesia for ambulatory surgery: A review of the available studies.Anaesth Crit Care Pain Med 2016 ; 35(6):417-421. DOI: 10.1016/j.accpm.2016.03.005

14. Routray SS, Raut K, Pradhan A, Dash A, SorenM. Comparison of Intrathecal Clonidine and Fentanyl as Adjuvant to Hyperbaric Bupivacaine in Subarachnoid Block for Lower Limb Orthopedic Surgery.Anesth Essays Res .2017 ; 11(3): 589– 593.doi: 10.4103/aer.AER_91_17.

15. Qurban F, Qureshi SA, Hassan SI, Azeem Y. Determine the analgesic effectiveness of Dexmedetomidine with hyperbaric bupivacaine in spinal anesthesia for patients undergoing lower limb surgery. Pak J Med Health Sci 2020;14(2):1569-71

16. Farooq S, Rizvi MFA, Yousuf SMA, Dilshad R, Bashir G, Dilshad A. Comparing intrathecal dexmedetomidine and fentanyl as adjuvants to hyperbaric bupivacaine in elective casarian section, a study. Professional Med J 2022; 29(2):218-226. doi.org/10.29309/TPMJ/2022.29.02.6414

17. Chaney MA. Side effects of intrathecal and epidural opioids. Can J Anaesth1995; 42:891-903. doi: 10.1007/BF03011037

18. Bi YH, Cui XG, Zhang RQ, Song CY, Zhang YZ. Low dose of dexmedetomidine as an adjuvant to bupivacaine in cesarean surgery provides better intraoperative somato-visceral sensory block characteristics and postoperative analgesia. Oncotarget 2017;8(38):63587-63595.doi: 10.18632/oncotarget.18864.

19. Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD, Alameddine MM, Al-Yaman R, et al. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta Anaesthesiol Scand 2006; 50:222-7.

20. Samantaray A, Hemanth N, Gunnampati K, Pasupuleti H, Mukkara M, Rao MH. Comparison of the effects of adding dexmedetomidine versus midazolam to intrathecal bupivacaine on postoperative analgesia. Pain Physician 2015;18(1):71–77

21. Bae HB. Dexmedetomidine: an attractive adjunct to anesthesia. Korean J Anesthesiol 2017;70(4):375-376. doi:10.4097/ kjae.2017.70.4.375

22. Naaz S, Ozair E. Dexmedetomidine in current anaesthesia practice- a review.J Clin Diagn Res 2014 ; 8(10):GE01-4.doi: 10.7860/JCDR/2014/9624.4946.

23. Patro SS, Deshmukh H, Ramani YR, Das G. Evaluation of Dexmedetomidine as an Adjuvant to Intrathecal Bupivacaine in Infraumbilical Surgeries. J Clin Diagn Res 2016;10(3): UC13-UC16.doi: 10.7860/JCDR/ 2016/ 17987.7379.

24. Gautam B, Lama SM, Sharma M. Effects of Adding Intrathecal Dexmedetomidine to Hyperbaric Bupivacaine for Saddle Spinal Block in Adults Undergoing Peri-anal Surgeries. J Nepal Health Res Counc 2018 ;16(1):43-48.

25. Rai A, Bhutia MP. Dexmedetomidine as an Additive to Spinal Anaesthesia in Orthopaedic Patients Undergoing Lower Limb Surgeries: A Randomized Clinical Trial Comparing Two Different Doses of Dexmedetomidine. J Clin Diagn Res 2017;11(4):UC09-UC12. doi: 10.7860/JCDR/ 2017/ 26241 .9654

Original Article **Open Access**

Clinical Outcome of Preterm Neonates with Respiratory Distress Syndorme on Continuous Positive Airway Pressure

Sijad-Ur-Rehman, Quratulain, Wahid Ali, Romana Bibi, Sohail Ashraf, Kulsoom Iqbal

ABSTRACT:

Objectives: To evaluate the clinical course in preterm neonates with Respiratory Distress Syndrome on bubble Continuous Positive Airway Pressure along with their outcome during stay in hospital.

Study Design and Setting: A descriptive case study at the NICU was carried out at Bacha-Khan Medical Complex Swabi from December 2020 to December 2021.

Methodology: Respiratory Distress Syndrome was diagnosed by following the criteria: tachypnea (> 60 breaths/min), subcostal retraction and saturation <92%. Clinical course was assessed by mean length of hospital stay from the day of admission to the day of discharge. Outcome was assessed by means of switching the baby to mechanical ventilation by failing CPAP therapy by not maintaining O_2 saturation > 92% and tachypnea > 60 breaths/min on 10cm maximum pressure of H_2O. CPAP response were noted.

Results: Total of 100 patients enrolled in our study, 56 patients were male and 44 patients were female. Mean age was 1.24+0.04days. Mean gestational age of babies was 31.18+0.170weeks. Mean weight of babies was 2.035+0.023kg. Mean hospital stay was 15.05+0.237days. Out of 100 patients included in study 76% babies needed ventilatory support during hospital stay and 24% babies recovered from respiratory distress syndrome without need of ventilator support.

Conclusion: Respiratory Distress Syndrome is a fatal complication in Preterm neonates in Neonatal Intensive Care Unit. Respiratory assistance done through continuous positive airway pressure has shown encouraging results in management by preventing complications, mechanical ventilation need, less hospital stay and preventing mortality.

Key Words: Respiratory Distress Syndrome, Continuous Positive Airway Pressure, Mechanical Ventilation.

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INTRODUCTON:

Leading causes of infant death and morbidity is respiratory distress syndrome. The illness known as RDS (respiratory distress syndrome in newborns) affects infants whose lungs have not yet reached their fully developed. It could also be attributed to hereditary difficulties with lung development. RDS is most common in babies born before the ages of 34 weeks.[1] At least two of the following clinical signs are required to diagnosis respiratory distress syndrome (RDS): tachypnea (>60/min), dyspnea with dyspnea, and dyspnea with Nasal retractions, subcostal or intercostal retractions, and inspiratory subcostal or intercostal retractions In room air, there is flaring, expiratory grunting, and cyanosis.[2] Severe respiratory distress syndrome (RDS), which is more common in preterm babies of less than 34 weeks, is one of the most common causes of this respiratory failure. It is usually caused by meconium aspiration syndrome in term infants and surfactant deficiency in premature babies.[3]

In Malawi, using the bCPAP to support newborns' ventilation is a very cost-effective method,[4] treatment of infant respiratory distress with a low-cost B-CPAP system has been shown to improve overall survival. The benefits were higher for infants with a low birth weight and RDS.[4,5] Bubble CPAP is a

significant advancement in the treatment of respiratory distress.[6,7] There was a considerable improvement in the mean respiratory rate, mean oxygen saturation (p=0.001), and frequency of chest in-drawing after 24 hours of bubble CPAP (p=0.001). In a Pakistani study, therapeutic efficacy was shown to be 80 (84.2%), and bubble CPAP may be utilized as the first line of respiratory support for preterm and extremely preterm newborns with RDS.[8] According to a recent study, this therapy is effective in avoiding respiratory problems in premature newborns.[9] According to Simone Martin's study, the bubble CPAP had a decreased failure rate for CPAP in these same studies in terms of mortality and complications (p=0.003).[10]

The rationale of this study is to evaluate the clinical outcome on bubble CPAP of premature neonates with respiratory distress syndrome as in literature we could not find such study conducted in Pakistan. Due to resource limitation, most of hospitals in our country lack facility of mechanical ventilator. This study will help to improve management of preterm neonates with RDS at resource limited hospital.
This study aimed to evaluate the clinical course in preterm neonates with RDS on bubble CPAP along with their outcome during stay in hospital.

METHODOLOGY:

A descriptive case study at the NICU was carried out at Bacha-Khan Medical Complex Swabi from December 2020 to December 2021. All premature infants admitted at gestational ages between 28-34 weeks included in inclusion criteria. NICU with RDS, birth weight <2500 grams, 3) either gender and exclusion criteria: babies with gross congenital anomalies, babies with gut and respiratory tract anomalies, Co-morbidities e.g. Infant of diabetic mother, hypoxic ischemic encephalopathy, preterm/premature rupture of membranes, antepartum hemorrhage.

Following institutional ethical approval from the Gajju Khan Medical College/Medical Complex Swabi 7-8/2022, 28038, chairperson of the institutional ethical review board, informed consent from parents, in the study, patients at the neonatal Intensive Care Unit at Bacha Khan Medical Complex Hospital Swabi who met the inclusion criteria after a comprehensive history and examination were included. Diagnosis of RDS was done by observing tachypnea (> 60 breaths/min), chest retractions and cyanosis at room air. Clinical course was assessed by mean length of hospital stay from the day of admission to the day of discharge. Outcome was assessed by means of switching of the baby to mechanical ventilation after 72 hrs of bubble CPAP therapy based on following criteria of not maintaining O_2 saturation > 92% and tachypnea > 60 breaths/min.

Mean and standard deviation were calculated for age ,period of gestation, weight in kg and duration of hospital stay, while frequency and percentages were calculated for gender and need of ventilator support.

RESULTS:

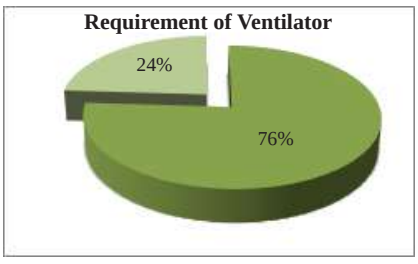
Total of 100 patients were enrolled in the study who presented in NICU, Bacha Khan Medical Complex Hospital after preterm birth. Among all the patients 56 patients were male and 44 patients were female. Descriptive statistics of age of all patients showed minimum age of 01 day and maximum age was 02 days. Mean age was 1.24+0.042 days. Minimum gestational age of patients was 28 weeks and maximum gestational age was 34 weeks. Mean gestational age of babies was 31.18 + 0.170 weeks.

Mean weight of babies was 2.03+0.023 kg. Minimum weight of baby was 1.5 Kg and maximum weight was 2.4 Kg. Minimum days of hospital stay were 11 days and maximum duration of stay was 22 days. Mean hospital stay was 15.05+0.237 days. Out of 100 patients included in study 76% babies needed ventilator support during hospital stay and 24% babies recovered from respiratory distress syndrome without needing ventilator.

DESCRIPTIVE STATISTICS

Gender	Frequency	Percentage	Probability	Requirement of Ventilator	Frequency	Percentage	Probability
Male	56	56%	0.56	Yes	76	76%	0.76
Female	44	44%	0.44	No	24	24%	0.24
Total	100	100%	1.00		100	100%	1.00

Pie Chart No. 01: Distribution of Patients Needing Ventilator Support



DISCUSSION:

Early detection of Respiratory Distress Syndrome (RDS) and management is key to prognosis of the disease. Marked tachypnea and low oxygen saturation are the main clinical indicators for diagnosis. Management is based on ensuring a secure airway and ventilation to improve on going pathology. Ventilation mainly invasive mechanical ventilation has been backbone of treatment for long but this method has been related to many complications and morbidity.

Alternate therapy in form of CPAP has been introduced in last few decades which can be in form of bubble CPAP and has shown improved results, less duration of stay in hospital and less need of invasive mechanical ventilation in patients receiving CPAP.[11] In a study conducted in Pakistan, successful treatment (efficacy) was found to be 80 (84.2%).[8] A recent study shown that this therapy is useful in reducing respiratory issues in late preterm infants. In our study improved outcome following CPAP use was seen with average stay of patients was 15.05+0.237days. Out of 100 patients included in study 76% babies needed ventilator support during hospital stay and 24% babies recovered from respiratory distress syndrome without needing ventilator support.

In hospitalized infants aged 28 days, CPAP was used to treat respiratory distress. The study, Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) and Newcastle-Ottawa Quality Assessment Scale techniques were used to assess the quality of recommendations. In three studies, using bubble CPAP first, rather than oxygen treatment, and then if necessary, mechanical ventilation reduced the need for mechanical ventilation by 30%-50%. Despite the fact that a meta-analysis of CPAP failure demonstrated that an Additional three trials comparing bubble CPAP to ventilator CPAP found that both groups' mortality and complication rates were the same (p=0.003).[11]

A retrospective analysis of neonates >32 weeks of gestation who were conveyed in Western Australian Neonatal Transport Service with acute respiratory distress. CPAP use grew dramatically from 33% in 2002 to 59% in 2004 over the study period. Overall, 10(29%) patients required endotracheal tube (ETT) ventilation, 166(45%) required nasal CPAP, and 95(26%) required cot oxygen. Within 24 hours, 22(13%) of the neonates in the CPAP group required ETT ventilation; these infants had a higher beginning those who were successfully transported on CPAP alone had lower oxygen requirements.[12]

In May 2006, a plan was created to encourage the use of bCPAP on a regular basis in neonates who require ventilator assistance to avoid intubation and Mechanical Ventilation. Intubation rates were found to be significantly different 72% (p<0.000). The proportion of patients treated only with bCPAP 27% (p=0.0001). Although the average duration of stay in the NICU increased (14.6 days in 2006 and 17.5 days in 2008, p=0.0481), the death rate was drastically lowered 40% (p=0.0001).[13]

Since it was initially introduced as an RDS is being treated with an interventional treatment, there have always been concerns about the increased labored breathing in neonates treated with nasal continuous PAP (n-CPAP). As a result, respiratory support systems such as nasal bi-level PAP (N-BiPAP) and sigh-PAP (SiPAP) were developed in the last ten years. From October 2012 to March 2014, a randomized clinical trial was conducted on 74 babies with RDS who were admitted in the NICU at Al-Zahra Hospital. Patients were randomized to one of two respiratory support groups: N-BiPAP or SiPAP, at random. Each group consisted of 37 neonates who were compared in terms of noninvasive ventilation duration and demographic features. In terms of the average length of noninvasive respiratory support and the average duration of the need for oxygen supplementation, there was no significant difference between the groups.[14]

In four rural Ghana hospitals, In the first hour, The mean respiratory rate of children who received immediate CPAP decreased by 16 breaths per minute (CI 95%: 10-21), compared to no change in children who received CPAP one hour later (CI 95%: -2 to +5).[15] A research was carried out in terms of demographics, CPAP failure (21.1 and 20.0% for VF and CF; p=1.000) did not differ between the groups, air leak syndrome (10.5 and 5.0%; p = 0.605), total CPAP time (median: 22.0 h, IQR: 8.00-31.00 h and median: 22.0 hour, IQR: 6.00-32.00 hour; p = 0.822).[16]

In a resource-limited situation, RDS in newborns were treated with a low-cost self-contained bubble System of bCPAP. In 2013, study in Blantyre, Malawi, patients experiencing respiratory distress weighing less than 10 kg were included in the study. 70% of those who were given bCPAP survived. Within 24 hr, 80% survivors showed signs of improvement. The use of bCPAP was judged to be beneficial by all treating physicians, resulting in a change in practice.[17]

CPAP was linked to a lower risk of treatment failure (typical risk ratio (RR) 0.64, 95 percent confidence interval (CI) 0.50 to 0.82; typical risk difference (RD) -0.19, 95% CI -0.28 to -0.09; decrease in the need for ventilator support (average RR 0.72, 95% CI 0.54 to 0.96; typical RD -0.13, 95% CI -0.25 to -0.02.[18] 37 infants with RDS were divided into two groups and given CPAP alone or CPAP plus HFOV treatment. Compared to the HPA+CPAP group, the CPAP group had longer mean scores for the duration of CPAP and oxygenation, as well as for the length of hospitalization. However, the differences were only statistically significant for the duration of oxygenation (P=0.05).[19]

In Kenya prematurity/acute respiratory distress syndrome was the most common indication, and the overall mortality rate was 24%. 61%of premature with acute respiratory distress syndrome being the most common indication for CPAP[20]. Prophylactic use of Bubble CPAP reduces the time it takes to alleviate respiratory distress (3.14+2.74 vs. 3.58+2.12 days, p-value > 0.05), as well as the incidence of RDS (40% vs. 46 %, p-value > 0.05), the need for surfactant (20% vs. 28 %), and the switch to mechanical ventilation (14% vs. 18 %, p-value > 0.05). Both groups had received prenatal steroids in about 80% of cases. BCPAP use as a preventive shortens hospital stays (28.34+12.18days vs. 30.74+12.24 days), increases sepsis frequency (22% vs. 18 %), and reduces the number of ROP (16% vs 22%).[21]

A study from Multan, Pakistan, Out of 172 newborns, 91 (52.9%) were malnourished, 89 (51.7%) had gestational ages between 31 and 32 weeks, and 97 (56.4%) were born weighing between 1000 and 1500 grams. The majority of the neonates, 97 (56.4%), had RDS that was radiological rated as moderate. 143 (83.1%) newborns experienced a successful outcome from early CPAP. There was no statistically significant difference in the results of the CPAP between the genders of research participants (p=0.4990). Birth weight, gestational age, and the degree of radiological grading of RDS were all substantially related to the effectiveness of CPAP (p=0.00001). Additionally substantially linked with CPAP outcomes among study participants were the arterial blood gas parameters PO2, PCO2, and HCO3 (p=0.0001).[22]

Another study from India was reported, 245/330 newborns were weaned from CPAP ventilation and released, while 85 babies passed away from the sickness. Infants with septicemia had a higher mortality rate. 25.75 percent of B-CPAP users had a Downes score of 4, 33.03 percent had a score of 5, and 41.21 percent had a score of 6. With the use of B-CPAP, all parameters, including cyanosis, grunting, tachypnea, chest indrawing, and air entry, improved. Asphyxia, RDS, prematurity-related apnea, meconium aspiration syndrome (MAS), and bronchopneumonia sepsis were some of the causes of respiratory distress.[23] According to another study, delivery room CPAP was linked to respiratory problems and the highest likelihood of NICU admission (9.3 times the risk of those without delivery room positive pressure).[24] Jordan published a different study that 143 infants in all (mean birth weight: 2,770–1,800 g) were enrolled. A newborn's brief tachypnea (42%), followed by a lengthy respiratory transition, was the most frequent underlying cause of respiratory distress (34%). Only nine newborns failed bCPAP, giving the therapy a success rate of 93.7%.[25]

In a research by Ramin Iranpour et al,[26] 4/34 (11.8%) preterm newborns who were treated with NCPAP for respiratory distress syndrome required a ventilator. Only 8 (13.3%) newborns needed mechanical ventilation, according to a study done in Pakistan. Overall, 52 babies were successfully weaned off of nCPAP. RDS (65%) was the main indicator of CPAP use.[27] 90 infants with a clinical diagnosis of RDS were studied in Islamabad. Starting CPAP for the treatment of RDS occurred at a mean age of 5.27+2.66 hours of life. Chest X-ray results for 11/90 newborns (11.22%) indicated severe RDS, while the results for the remaining 79 babies (88.78%) indicated mild to moderate RDS.[28] In another Pakistani study, At 24 hours, the B-CPAP had 100% of the projected survival rates. Following 48 hours, the comparable outcomes were all positive.[29] Another study carried out in Multan, Out of 172 newborns in total, 97 (56.4%) had radiological RDS to be moderate, 143 (83.1%) newborns showed successful results with early CPAP.[30]

Limitations of our study were single centered study data collected form the neonates admitted in our department and poor maternal efforts. Majority of the neonates who were born premature in periphery were presented late and were not treated properly by getting the appropriate dose of treatment they needed. The mortality and morbidity of infants who are born premature and with low birth weights should all be prevented by using CPAP and timely treatment if they experience respiratory distress syndrome.

CONCLUSION:

Respiratory Distress Syndrome is frequent and fatal condition seen in Preterm neonates in NICU. Early and prompt treatment is main stay of management. Respiratory assistance done through continuous positive airway pressure has shown encouraging results in management by preventing complications like need of mechanical ventilation, less hospital stay and preventing mortality. More studies need to be done with larger population size to extensively see the long terms outcome of this mode of treatment.

Authors Contribution:
Sijad-Ur-Rehman: Manuscript Writing, Concept of Study and Data Collection
Quratulain: Literature Review, Data Analysis
Wahid Ali: Manuscript Writing
Romana Bibi: Manuscript Writing, Data Analysis, Critical Review and Corresponding Author
Sohail Ashraf: Results Interpretation and Discussion Writing
Kulsoom Iqbal: Study Designing, Study Conduction

REFERENCES:

1. Groenendaal F, De Vries LS, Martin RJ, Fanaroff AA, Walsh MC. Hypoxic-ischemic encephalopathy. Fanaroff and Marfin's neonatalperinatal medicine. Diseases of the fetus and infant. 2015:904-26.
2. Balamkar R and Shrikhande D (2015) Surfactant Replacement Therapy in Neonatal Respiratory Distress Syndrome: Case Control Study in Rural Hospital, Loni, India. Resea J of Pharma, Biol and Chemi Sci, 2015 6(5): 1123-28
3. Pooniya V. Management of neonatal respiratory distress syndrome by indigenous CPAP in a resource poor setting. J Pediatr Care 2015;1:1.
4. Kawaza K, Machen HE, Brown J, Mwanza Z, Iniguez S, Gest A, et al. Efficacy of a low-cost bubble CPAP system in treatment of respiratory distress in a Neonatal Ward in Malawi. PLoS ONE 2014;9(l):e86327. DOIhttps://doi.org/ 10.1186 /s12887-014-0288-1
5. Dewez JE, van den Broek N. Continuous positive airway pressure (CPAP) to treat respiratory distress in newborns in low-and middle-income countries. Tropical Doctor 2017; 47(1):19-22.
6. Chen A, Deshmukh AA, Richards-Kortum R, Molyneux E, Kawaza K, Cantor SB. Cost-effectiveness analysis of a low-cost bubble CPAP device in providing ventilatory support for neonates in Malawi – a preliminary report. BMC Pediatr 2014; 14:288. doi: 10.1186/s12887-014-0288-1.

7. Brown J, Machen H, Kawaza K, Mwanza Z, Iniguez S, Lang H. A high-value, low-cost bubble continuous positive airway pressure system for low-resource settings: technical assessment and initial case reports. PLoS One 2013; 8(1):e53622. doi.org/10.1371/journal.pone.0053622. doi.org/10.1371/journal.pone.0090972
8. BANO I, HAROON F, MALIK KB, Bari A, Rathore AW. Efficacy of Nasal Continuous Positive Airway Pressure by Bubble CPAP in Neonates with Respiratory Distress Syndrome. Pak Pediatr J. 2021;45(4):384-88.
9. Gyamfi-Bannerman C, Thom EA. Antenatal Betamethasone for Women at Risk for Late Preterm Delivery. N Engl J Med. 2016;375(5):486–7. pmid:27518669. DOI: 10.1056/NEJMoa1516783
10. Martin S, Duke T, Davis P. Efficacy and safety of bubble CPAP in neonatal care in low and middle income countries: a systematic review. Arch Dis. Child Fetal Neonatal Ed. 2014; 99: 495-504. doi.org/10.1136/archdischild-2013-305519
11. Jobe AH, Ikegami M. Biology of surfactant. Clin. Perinatol. 2001; 28:655. doi.org/10.1016/S0095-5108(05)70111-1
12. Resnick S, Sokol J. Impact of introducing binasal continuous positive airway pressure for acute respiratory distress in newborns during retrieval: Experience from Western Australia. J. Paediatr. Child Health. 2010; 46:754-9. doi.org/10.1111/j.1440-1754.2010.01834.x
13. Rezzonico R, Caccamo LM, Manfredini V, Cartabia M, Sanchez N, Paredes Z, et al. Impact of the systematic introduction of low-cost bubble nasal CPAP in a NICU of a developing country: a prospective pre- and post-intervention study. BMC Pediatr. 2015;15:26.
14. Sadeghnia A, Danaei N, Barkatein B. A Comparison of the Effect of Nasal bi-level Positive Airway Pressure and Sigh-positive Airway Pressure on the Treatment of the Preterm Newborns Weighing Less than 1500 g Affiliated with Respiratory Distress Syndrome. Int. J. Prev. Med. 2016;7:21. doi: 10.4103/2008-7802.173930
15. Wilson PT, Morris MC, Biagas KV, Otupiri E, Moresky RT. A randomized clinical trial evaluating nasal continuous positive airway pressure for acute respiratory distress in a developing country. J. Pediatr. 2013; 162:988-92. doi.org/10.1016/j.jpeds.2012.10.022
16. Yagui AC, Vale LA, Haddad LB, Prado C, Rossi FS, Deutsch AD, et al. Bubble CPAP versus CPAP with variable flow in newborns with respiratory distress: a randomized controlled trial. J Pediatr. (Rio J). 2011; 87:499-504.
17. Machen HE, Mwanza ZV, Brown JK, Kawaza KM, Newberry L, Richards-Kortum RR, et al. Outcomes of patients with respiratory distress treated with bubble CPAP on a pediatric ward in Malawi. J. Trop. Pediatr. 2015;6:421-7. doi.org/10.1093/tropej/fmv052
18. Ho JJ, Subramaniam P, Davis PG. Continuous positive airway pressure (CPAP) for respiratory distress in preterm infants. Cochrane Database of Systematic Reviews. 2020(10). doi.org/10.1002/14651858.CD002271.
19. Choupani Dastgerdi R, Hamidi M, Khalili Dehkordi M. Comparison of the Effectiveness of Continuous Positive Airway Pressure (CPAP) Therapy with a Combination of High-Frequency Oscillations and CPAP in the Treatment of Respiratory Distress Syndrome in Infants. IJN. 2022;13(1):13-7. https://ijn.mums.ac.ir/article_19523.html
20. Olayo B, Kirigia CK, Oliwa JN, Agai ON, Morris M, Benckert M, Adudans S, Murila F, Wilson PT. Effective training-of-trainers model for the introduction of continuous positive airway pressure for neonatal and paediatric patients in Kenya. Paedr inter child healt. 2019 ;39(3):193-200. doi.org/10.1080/20469047.2019.1624007
21. Shaheen M, Jahan I, Hossain MI, Rahaman MM. Use of bubble continuous positive airway pressure (bCPAP) for prevention of respiratory distress in preterm infants; Eur J Pharm Med Resea:2021,8(4), 643-648
22. Rehman A, Quddusi AI, Nadeem A, Fatima N, Iqbal I. Early nasal continuous positive airway pressure in preterm neonates with Respiratory Distress Syndrome. The PMJ. 2021; 28(07):957-62. DOI:https://doi.org/1 0.29309/TPMJ/2021.28.07.5707
23. Slain KN, Rotta AT, Martinez-Schlurmann N, Stormorken AG, Shein SL. Outcomes of children with critical bronchiolitis meeting at risk for pediatric acute respiratory distress syndrome criteria. Pediatr Crit Car Med. 2019;20(2):e70-6. DOI:10.4103/jpai.jpai_11_21
24. Spillane NT, Macalintal F, Nyirenda T, Golombek SG. What happens to 35 week infants that receive delivery room continuous positive airway pressure?. Journal of Perinatology. 2021 ;41(7):1575-82. doi.org/10.1038/s41372-020-00883-w
25. Al-Lawama M, Alkhatib H, Wakileh Z, Elqaisi R, AlMassad G, Badran E, Hartman T. Bubble CPAP therapy for neonatal respiratory distress in level III neonatal unit in Amman, Jordan: a prospective observational study. Int J Gen Med. 2019;12:25. doi: 10.2147/IJGM.S185264
26. Iranpour R, Armanian AM, Abedi AR, Farajzadegan Z. Nasal high-frequency oscillatory ventilation (nHFOV) versus nasal continuous positive airway pressure (NCPAP) as an initial therapy for respiratory distress syndrome (RDS) in preterm and near-term infants. BMJ Paediatr Open. 2019: 14;3(1):e000443. doi: 10.1136/bmjpo-2019-000443. PMID: 31414062; PMCID: PMC6668751.
27. Anwaar O, Hussain M, Shakeel M, Baig MM. Outcome of use of nasal continuous positive airway pressure through infant flow drivers in neonates with respiratory distress in a tertiary care hospital in Pakistan. Journal of Ayub Medical College Abbottabad. 2018: 26;30(4):511-5.
28. Zia J, Zaman N, Zafar A, Mumtaz H, Fazal S. Early Bubble Continuous Positive Airway Pressure Therapy for Premature Neonates with Respiratory Distress Syndrome. Annals of PIMS. 2022: 28;18(1):41-5.
29. Khan G, Imtiaz S, Farooq K, Hamza A, Roy S, Imran M. Comparison of Bubble Continuous Positive Airway Pressure Versus Conventional Ventilation In Neonates with Respiratory Distress Syndrome. PJMHS. 2022 26;16(04):811-.
30. Rehman A, Quddusi AI, Nadeem A, Fatima N, Iqbal I. Early nasal continuous positive airway pressure in preterm neonates with Respiratory Distress Syndrome. The PMJ. 2021: 10;28(07):957-62.

Original Article **Open Access**

Correlation of Uroflowmetry with Prostate Volume and International Prostatic Symptom Score (IPSS)

Iffat Raza, Nausheen Jamshed, Mubina Lakhani, Maria Mohiuddin, Syeda Bushra Ahmed, Sahrish Mukhtar

ABSTRACT

Objective: To correlate Uroflowmetry with Prostate volume and International Prostatic Symptom Score in BPH patients and healthy adults in a subset of Karachi Population.

Study Design and Setting: This is a crossectional study carried out at Ziauddin Hospital, Karachi over a period of 6 months.

Methodology: In this study 100 Samples were taken through non probability convenience sampling. Inclusion criteria includes 40years and above. Sample initially was taken on the basis of International Prostatic Symptom Score i.e., less than 8 and greater than 8 score. Ultrasonography was performed. 65 Individuals with International Prostatic Symptom Score > 8 and Prostate volume <25 and individuals having symptom index < 8 and Prostate volume > 25ml went for Uroflowmetry. Mean and standard deviation was taken out for quantitative variables. Univariate analysis and Multiple Linear Regression applied to assess relationship between Uroflowmetry with Prostate volume and International Prostatic Symptom Score.

Result: Mean age of patients was found to be 58±6 years. Mean International Prostatic Symptom Score was 11±4. Mean Prostate Volume was 28ml±5, mean Qmax was 14ml/s ±4. The correlation between Qmax and International Prostatic symptom score was found to be negative (-0.78) and statistically significant. No correlation was found between Prostate volume and Qmax.

Conclusion: Qmax and International Prostatic Symptom Score are reliable tool for assessing Benign Prostatic Hyperplasia patients concluding that as Symptom Score increases Qmax decreases. Qmax showed no correlation with Prostate volume**.** Prostate volume assessed on Ultrasonography is not an authentic parameter for diagnosing BPH patients**.**

Keywords: International Prostatic Symptom Score (IPSS), Prostate volume (PV), Lower Urinary Tract Symptoms (LUTS), Uroflowmetry (UFM), Qmax (peak flow measurement)

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INTRODUCTION:

Benign Prostatic Hyperplasia, the most frequently occurring disease among aged males of 40 to 80 years[1]. It is important to evaluate prostate volume of individuals with BPH that have symptoms of lower urinary tract as if it is not treated timely will worsen the condition leading towards Urinary Retention. Prostate Volume (PV) is important predictor as well as prognostic factor for minimally invasive Transurethral Prostatectomy and open prostatectomy[2]. In order to diagnose BPH, prostate volume assessed by Transabdominal Ultrasonography (TAUS) was the most easily available and accessible parameter, however reliability was always a concern, thus Transrectal Ultrasonography (TRUS) is usually considered as gold standard for diagnosing BPH[3].

Uroflowmetry (UFM) is a simple, noninvasive procedure that measures the flow rate of voided urine. Its use has become clinically widespread. Turner Warwick was the first to demonstrate how I/V urogram can be replaced into a urodynamic study[4]. It measures the flow of urine during

urination. Patient urinates in a funnel or commode that is connected to an instrument that measures urinary flow. It is converted into a graph and doctor interprets its report. UFM gives interpretation of peak flow rate, average flow rate, time to peak flow, flow time, voiding time and voided volume is calculated as milliliters of urine passed per second[5]

McConnell's practice guidelines have described that 125 to 150 ml minimum should be the voided volume to have accurate Uroflowmetry readings. Peak flow measurement (Qmax) of <10 ml/s is diagnosed as 'clinically obstructed Benign Prostatic Hyperplasia (BPH) patient[6]. The most characteristic finding in Uroflowmetry of Benign Prostatic Hyperplasia is decreased maximal flow rate (Qmax) that results in decreased urinary flow causing urinary retention that consequence to bladder stone formation and infections of urinary tract.

According to another study, maximal flow rate (Qmax) is the single best criterion for evaluating patients with BPH before embarking on any medical or surgical treatment[7]. Uroflowmetry is performed using a flow meter to measure the quantity of fluid voided per unit of time (expressed in milliliter per second (ml/s)[7]. Uroflowmetry is performed in a routine clinical practice to early diagnose BPH in an OPD setting but its result might vary with aging, washroom settings for UFM machine, cultural background, psychosocial issues and detrusor muscle instability. The gold standard for evaluating grade of lower urinary tract symptoms is urodynamic studies with pressure-flow analysis. Flow rate measurements like Uroflowmetry are nowadays used in clinics along with ultrasonography of the LUT[8].

International Prostatic Symptom Score (IPSS) is definitive questionnaire for initial assessment of inpatients having LUTS. This score is beneficial after TURP for post treatment monitoring of symptoms[8] and can be used as a tool for selection of treatment modalities, to assess treatment response and follow up after open prostatectomy or after alpha blockers administration[9]. "IPSS is based on the answers to 7 questions (Frequency, Urgency, Nocturia, Incomplete emptying, Intermittency, Weak stream and Straining). The answers are from 0 to 5. The total score ranges from 0 to 35 (asymptomatic to symptomatic). The Symptom index is categorized as mild (≤7), moderate (8-19) and severe (≥20)". Each question is further divided into 5 question 0. Not at all symptoms occurs, 1.less than 1 in 5 times 2. less than half the time 3.about half the time 4.More than half the time 5.Almost always , these symptoms are scored as zero to five[10].

The basic objective of this study was to determine that Uroflowmetry correlation (Qmax) with Prostate volume is more reliable, authentic and better than with UFM correlation with IPSS as questionnaire is readily available, being widely used by urologists in urology clinics for assessing Benign Prostatic Hyperplasia patients and healthy adults coming with lower urinary tract symptoms.

METHODOLOGY:

This study was conducted at Ziauddin University Hospital, Clifton Karachi for a period of six months from January to March 2018 after taking permission from ERC# 0010115I-RANA. The target population was 40 years and above. 100 Individuals were selected through nonprobability convenience sampling. Inclusion criteria includes male, 40 years and above. Exclusion criteria includes prostatitis, prostatic carcinoma, urinary retention, already taking prostatic medicine.

Sample size was calculated, keeping prevalence at 40%, confidence level of 95% and bound of error at 0.07%. $n=z^2 P(1-P)/B^2$

Participants were asked to fill biodata and IPSS questionnaire. On the basis of IPSS questionnaire, two groups were made i.e IPSS < 8 and IPSS >8. IPSS<8 was labeled as healthy adults and IPSS > 8 were labelled as patients along with already prior evidenced medical report of BPH were also included in >8 IPSS group.

After filling biodata and IPSS forms, respective individuals were sent for Transabdominal Ultrasonography on Ultrasound machine,Toshiba Xario version 0.09 ^{0}. Two groups were made on the basis of Prostate volume ,first group includes less than 25ml volume second group includes greater than 25 ml volume. After ultrasonography there were 65 individuals with IPSS > 8 and PV <25ml and 35 individuals with IPSS <8 and PV >25ml. These two groups included 100 patients falling in gray area zone were then referred for Uroflowmetry to assess the prognosis of BPH that is whether prostate volume is a diagnostic criterion or International Prostatic Symptom Score itself. PSA was not performed.

Uroflowmetry is performed in a urinal that is connected to a measuring device, it measures the flow and speed of urine coming out of the body and how much time is required for emptiness of bladder.

STATISTICAL ANALYSIS: It was a crossectional study and analyzed on SPSS version 23. Mean and standard deviation were taken out for the quantitative variables. Multiple linear regression test was done to find out linear relationship among the Qmax and prostate volume along with Qmax and IPSS. Bivariate Correlate was done to see correlation between Qmax and IPSS, Qmax with PV. p-value < 0.05 was considered statistically significant.

RESULT:

In present study mean IPSS was found to be 11.1, mean PV was found to be 28, mean Qmax was found to be 14 of 100 individuals that includes with PV less than 25 ml and IPSS greater than 8 and prostate volume greater than 25ml and IPSS less than 8 as shown in Table 1. Results obtained in correlation of UFM with International Prostatic Symptom

score and prostrate volume A Univariate analysis was conducted among Uroflowmetry variable Qmax and International Prostatic Symptom Score and between Qmax and Prostate Volume. r was determined using Pearson's correlation coefficient and p value was determined using ANOVA. We found a negative strong correlation of Qmax with IPSS with -0.782 with p value of 0.001 and found a positive moderate correlation between Qmax and Prostate volume with 0.315 with significant p value. Regression square linear variable came out to be 0.612. In this study mean value of peak flow rate (Qmax) was found to be 15ml/s, with a minimum recording of 6ml/s and maximum of 21ml/s. The mean average flow rate (Qmed) was found to be 7.1 ± 2 ml/s.

In this study, Pearson correlation test was applied between International Prostatic Symptom score with Qmax and significant negative correlation was found with Total IPSS whereas individual questions included in IPSS questionnaire were i.e Q.1 Incomplete emptying, Q2 Frequency, Q3, Intermittency, Q4 Urgency, Q5 Weak Stream, Q6 Hesitancy or Straining, Q7 Nocturia also showed correlation with Qmax.

Q4 urgency showed weak negative correlation with Qmax where moderate negative correlation coefficient was found to be r = -0.381 with significant p value = 0.00 , Q3 Intermittency also showed weak negative correlation with Qmax r = -0.106, p = 0.00 also found to be significant and Q7 Nocturia also showed significant moderate negative correlation with Qmax r= -0.461 and p = 0.00 also statistically significant .Rest of the questions of IPSS were statistically significant with Qmax but showed positive correlation.

Figure 01: Flow chart of Methodology of Study

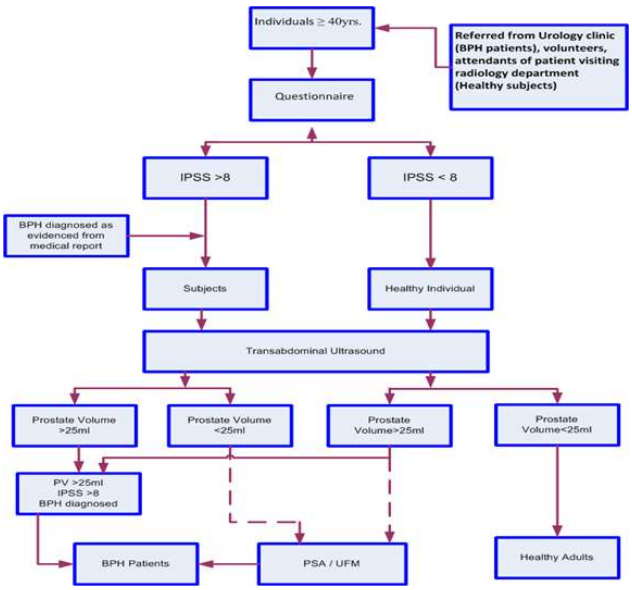

Table No 01: Descriptive Statistics

Total Uroflowmetry performed	*PV <25ml, IPSS >8*	*65 individuals*
N=100	*PV > 25 ml, IPSS <8*	*35 individuals*
Variable	*Mean*	*St. Deviation*
Age (years)	*58*	*6*
IPSS	11	4.3
Prostate Volume (ml)	28	5.4
Qmax (ml/s)	14	4

Table 02: Univariate analysis Of Qmax with IPSS & Prostate Volume

Qmax	I P S S	Prostate volume
Pearson Correlation (r)	-0.782	0.509
p-value	0.00	0.40

r was determined by Pearson correlation coefficient. R2 linear variable: 0.612
p value <0.05 considered statistically significant

Figure 02 : Graphical representation of Uroflowmetry

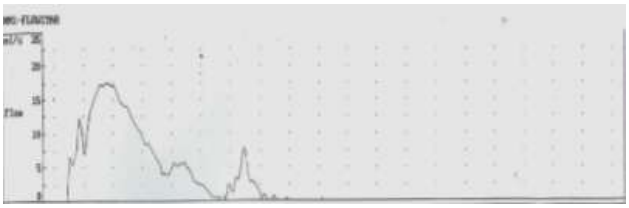

Figure 03: Showing peak flow rate = 17.5 ml/, voided volume =241m

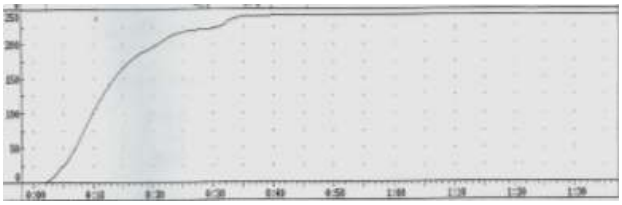

Table 3: IPSS correlation with Qmax

S.no	IPSS	r value	p-value
Q1.	Incomplete emptying/Qmax	.381	0.00
Q2.	Frequency/Qmax	0.461	0.00
Q3.	Intermittency/Qmax	-0.106	0.00*
Q4.	Urgency/Qmax	-0.318	0.00*
Q5.	Weak Stream/Qmax	0.11	0.413
Q6.	Hesitancy/Qmax	0.472	0.00
Q7.	Nocturia/ Qmax	-0.461	0.00*

r= Pearson correlation coefficient and p= <0.05 significant

DISCUSSION

In present study, 100 individuals were included BPH and healthy adults. Mean age found in our study was 58 ± 6 years (Table 1) which was also found in another study as Lower Urinary tract symptoms are common in this age group[12].

Mean International Prostatic Symptom Score found in our study was 11± 4 which came under moderate symptoms of lower urinary tract, this was also in accordance to other studies[13].

Mean Qmax obtained by Uroflowmetry was 14ml/s which was also seen in other studies and thus explaining unobstructed prostate[14].

In this study, we aimed to find out the reliability of IPSS with Qmax and also with PV at the same time in individuals suffering from lower urinary tract symptoms. Prostate volume less than 25ml and IPSS greater than 8, there were 65 individuals (Table 01) falling in this category where UFM was performed on these individuals to see whether Qmax itself standalone in diagnosing benign prostatic obstruction and also enables us to identify lower urinary tract symptoms in urology clinics. We found out that correlation of Qmax with IPSS and p value was statistically significant with r= -.782 respectively. In our study we found negative relationship of Qmax with IPSS (Table 3) therefore substantial the size of gland lower was the Qmax and greater the IPSS lower was peak flow rate. Our results were in consensus with Zamboan et al they also observed negative relationship between Qmax with prostate volume and IPSS[15] Singla et al also found negative correlation of Qmax with prostate volume as prostate enlarges Qmax is increasing rather instead of decreasing values and going towards obstruction however Qmax showed no correlation with prostate volume in our study. According to recent study published in 2022 they could not find any correlation between prostate volume and Qmax[16]. Another Nigerian study published in 2021 showed discordance and found out negative and statistically significant correlation between Qmax and prostate volume.

The 35 individuals having IPSS <8 and PV > 25ml these individuals underwent for UFM their Qmax came out to be greater than 15ml/s , these individuals were advised for follow up visit. These individuals were asked for further urodynamic testing after 2 weeks. Thus, prostate volume measured by ultrasonography is not a good measurable indicator to diagnose patients as benign prostatic hyperplasia. The most important parameter in uroflow study is the *Qmax*[17]. Shoukry *et al.* in their study, concluded that *Qmax* correlated well with the degree of prostatic obstruction[9]. The average flow rate is less reliable and the other values are immaterial. Traditionally, *Qmax* less than 10 mL/s indicates an obstruction and a *Qmax* greater than 15 mL/s indicates no obstruction[9]. The Qmax and the Qave are also used in identifying patients with Bladder Outlet Obstruction[18].

In this study most common clinical presentation as asked in IPSS questionnaire was urgency, intermittency and nocturia. We also found out in this study that IPSS correlated with Qmax. These findings were similar to another study[19] which observed that nocturia as the only most occurring , repeatable symptom also correlated with UFM i.e Qmax. Thus, we find inverse relationship of IPSS with Qmax[20]. Symptoms like urgency, intermittency and nocturia significantly correlated with Qmax and depict the most commonly occurring symptoms in BPH patients. According to study conducted in Abdul Wahab Hospital most commonly occurring symptoms were Incomplete Emptying occurring in 85% of patients visiting Clinics and 90% of patients had complaints of Nocturia[21]. Nocturia usually occurs in elderly as urinary bladder, prostate have more excitatory stimulation of parasympathetic innervation at night and decreased sympathetic inhibition resulting in contraction of urinary bladder along with prostatic enlargement and weak urethral muscle leads to frequent urination at sleeping hours. According to the study conducted in Turkish population, a negative correlation coefficient was found between Qmax and Urgency[22]. Urgency occurs when there is contraction of already contracted bladder also leading to incomplete emptying or residual volume.

According to the study conducted in 2017, intermittency was also one of the symptoms observed in patients with benign prostatic hyperplasia and bladder outlet obstruction[23]. Whereas, some studies on Asian men explains that lower urinary tract symptoms are most of the time associated with bladder outlet dysfunction, detrusor muscle instability and small prostate size and high peak flow rate (Qmax)[24]. Same results were observed in studies conducted in Japanese population and in Caucasian men where prostate volume was not significantly greater as compared to symptoms observed[24]. However, some studies do explain the benefit of transurethral prostatectomy even size of prostate is not larger enough thus helping patient in relieving their symptoms along with lowered IPSS[25]. Therefore, prostate volume can be one of the parameter to diagnose LUTS but prostate volume alone is not at all a reliability index for diagnosing BPH, instead Qmax can be beneficial.

Uroflowmetry provides a strong diagnostic tool and meaningful guidance for the surgeons and urologist so that necessary therapeutic medical and surgical procedures can be carried out on BPH patients and also helpful for individuals visiting clinics for lower urinary tract symptoms[25]. Regarding medical treatment, uroflowmetry of BPH patient if appears to be 15ml/s or below, then Initially alpha blockers are being prescribed but if patient is having erectile dysfunction along then phosphodiesterase inhibitors are prescribed instead. If symptoms do not improve and Qmax declines to <15ml/s then 5 alpha reductase inhibitors are recommended. Patient with Bladder Outlet Obstruction beta 3 agonist and anticholinergics are treatment of choice. If Qmax is <10ml/s then urodynamics test such as Cystoscopy and Uroflowmetry is mandatory and after that surgical intervention Transurethral resection of Prostatectomy(TURP) is carried out in these patients.

This study is done in a subset of a local population of Karachi representing the same results as with other international

population. However, there are emerging trends of Uroflowmetry internationally and our country is lacking behind in these, such as Acoustic Uroflowmetry mobile app available in which patient can monitor their readings in a diary. Visual Prostate Symptom Score(VPSS) is also readily available in urological clinics but not available in Pakistan for elderly and men with low education background.

The Professional significance of this study is based on IPSS cannot be alone used to assess lower Urinary tract Symptoms but instead Uroflowmetry is a diagnostic tool for assessing obstructive objective symptoms in Benign Prostatic Hyperplasia patients. Uroflowmetry helps urologist to decide therapeutic intervention in patients. IPSS and Uroflowmetry are affordable, readily available parameters and should be available in every urology clinic.

However, there were few limitations of this study. Transrectal ultrasonography (TRUS) is a newer technique and gold standard for diagnosis of prostate cancer. It provides clear image of organs in the pelvis, however we used Transabdominal sonography (TAUS) because TRUS requires patient tolerance and it is difficult to get consent from patient, due to our cultural norms. Disproportionate sample size for different groups, therefore our study sample might have been affected by selection bias.

Some of the future recommendations in this study includes that a large sample size cohort study should be conducted in order to get beneficial substantial results regarding individuals with higher IPSS and low prostate volume as there could be nonobstructive neurogenic mechanisms other than Benign prostatic hyperplasia. Other parameters of Uroflowmetry should be assessed which can help in making diagnostic tool easier.

CONCLUSION:

Uroflowmetry has been used to measure the peak flow rate (Qmax) which is the most important parameter in Uroflowmetry and one of the best options for assessing lower urinary tract symptoms (LUTS). IPSS is a quick assessment parameter in diagnosing BPH patients and showed significant inverse correlation with UFM that signifies that as Qmax decreases IPSS increases. Intermittency, Urgency and Nocturia are the most frequently occurring symptom that best correlated with Qmax. However, Qmax showed no correlation with prostate volume. The inexplicit details of prostate volume cannot help urosurgeons for decision making for TURP or open prostatectomy.

Authors Contribution:
Iffat Raza: Study Conduction and Manuscript writing
Nausheen Jamshed: Analysis
Mubina Lakhani: Critical Review
Maria Mohiuddin: Critical Review
Syeda Bushra Ahmed: Interpretation
Sahrish Mukhtar: Manuscript writing

REFERENCES:

1. Egan KB. The epidemiology of benign prostatic hyperplasia associated with lower urinary tract symptoms: prevalence and incident rates. Urologic Clinics. 2016;43(3):289-97. Https://doi.org/10.1016/j.ucl.2016.04.001
2. Omri N, Kamil M, Alexander K, Alexander K, Edmond S, Ariel Z, et al. Association between PSA density and pathologically significant prostate cancer: The impact of prostate volume. The Prostate. 2020;80(16):1444-9. Https://doi.org/10.1002/pros.24078
3. David RA, Badmus TA, Salako AA, Asaleye CM, Adeloye D, Fanimi O, et al. Diagnostic performance of transrectal ultrasound for prostate volume estimation in men with benign prostate hyperplasia. International Journal of Clinical Practice. 2020;74(11):e13615. Https://doi.org/10.1111/ijcp.13615
4. Bin Redzuan MZA. The effect of voiding position on uroflowmetry findings of patients with Benign Prostatic Hyperlasia (BPH) in urology clinic, Hospital Tengku Ampuan Afzan (HTAA), Kuantan, Pahang: Kuantan, Pahang: International Islamic University Malaysia, 2016; 2016.
5. Putra IBOW, Hamid ARAH, Rasyid N, Mochtar CA, Umbas R. Comparison of visual prostate symptom score with the international prostate symptom score and uroflowmetry parameters in assessing men with lower urinary tract symptoms in Dr. Cipto Mangunkusumo National General Hospital, Indonesia. Prostate International. 2019;7(3):91-5. Doi: 10.1016/j.prnil.2018.09.001
6. Gammie A, Rosier P, Li R, Harding C. How can we maximize the diagnostic utility of uroflow?: ICI-RS 2017. Neurourology and Urodynamics. 2018;37(S4):S20-S4. Https://doi.org/10.1002/nau.23472
7. Abrams P, Chapple C, Khoury S, Roehrborn C, De la Rosette J, Committee IS, et al. Evaluation and treatment of lower urinary tract symptoms in older men. The Journal of urology. 2009;181(4):1779-87. Doi: 10.1016/j.juro.2008.11.127.
8. Amu O, Udeh E, Ugochukwu A, Dakum N, Ramyil V. The value of international prostate symptom scoring system in the management of BPH in Jos, Nigeria. Nigerian journal of clinical practice. 2013;16(3):273-8. DOI: 10.4103/1119-3077.113446
9. Oranusi C, Nwofor A, Mbonu O. Correlation between international prostate symptom score and uroflowmetry in patients with benign prostatic hyperplasia. Nigerian Journal of clinical practice. 2017;20(4):454-8. Doi: 10.4103/1119-3077.196120.
10. Morey AF. Re: The International Prostate Symptom Score (IPSS) is an Inadequate Tool to Screen for Urethral Stricture Recurrence after Anterior Urethroplasty. The Journal of urology. 2017;197(5):1300-1. Https://doi.org/ 10.1016/j. juro. 2017.01.009
11. Raza I, Mukhtar S, Kamran M. Benign prostatic hyperplasia;: correlation of prostate gland volume with age & anthropometric parameters in patients. The Professional Medical Journal. 2017;24(03):445-52. Http://dx.doi.org/ 10.17957/ TPMJ/17. 3696
12. Eldib DB, Moussa AS, Sebaey A. Evaluation of different MRI parameters in benign prostatic hyperplasia-induced bladder outlet obstruction. Egyptian Journal of Radiology and Nuclear Medicine. 2019;50(1):1-10.

13. Jiang Y-H, Lin VC-H, Liao C-H, Kuo H-C. International Prostatic Symptom Score—voiding/storage subscore ratio in association with total prostatic volume and maximum flow rate is diagnostic of bladder outlet-related lower urinary tract dysfunction in men with lower urinary tract symptoms. Plos One. 2013;8(3):e59176. Doi: 10.1371/journal.pone.0059176.

14. Kasraeian A, Alcantara M, Alcantara KM, Altamirando JA. Aquablation for BPH. The Canadian Journal of Urology. 2020;27(5):10378-81. PMID: 33049190

15. Zambon JP, Batezini nsds, Karam Junior AJ, Conceicao RDO, Carvalho jamd, Almeida FG. Uroflowmetry in a Large Population of Brazilian Men Submitted to a health check up program and its correlation with ipss and prostate size. International braz j urol. 2013;39:841-6. DOI: 10.1590/S1677-5538.IBJU.2013.06.10

16. Sanman K, Patil S, Prabhu GL, Shetty R, Venugopal P. Prostate Disease Severity Score: In the management of benign enlargement of prostate. Journal of Clinical Urology. 2022 doi: 20514158221078468.

17. Setthawong V, Mahawong P, Pattanachindakun N, Amnattrakul P, Dar FM, Thanavongvibul S. To investigate the correlation between the visual prostate symptom score, the international prostate symptom score, and uroflowmetry parameters in adult Thai males of different educational levels. Prostate international. 2018;6(3):115-8. Https://doi.org/ 10.1016/j.prnil.2017.12.001

18. Lee KS, Song PH, Ko YH. Does uroflowmetry parameter facilitate discrimination between detrusor underactivity and bladder outlet obstruction? Investigative and clinical urology. 2016;57(6):437. DOI: 10.4111/icu.2016.57.6.437

19. Tikkinen KA, Johnson TM, Tammela TL, Sintonen H, Haukka J, Huhtala H, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. European urology. 2010;57(3):488-98. DOI: 10.1016/j.eururo.2009.03.080

20. Kajimotu T, Bowa K. Accuracy of a "Single Question Nocturia Score" compared to the "International Prostate Symptoms Score" in the evaluation of lower urinary tract symptoms in benign prostatic hyperplasia: A study performed at Ndola Teaching Hospital, Ndola, Zambia. Plos one. 2018;13(6):e0198096. Https://doi.org/ 10.1371/ journal. pone. 0198096

21. Ramadhanurrosita N, Soebhali B, Nugroho H. The correlation of international prostate symptom score (ipss) with qmax on uroflowmetry of benign prostatic hyperplasia (bph) patients at abdul wahab sjahranie hospital in samarinda. Jurnal Ilmu Kesehatan. 2019;7(2):85-91. Https://doi.org/ 10.30650/jik.v7i2.288

22. Keskin MZ, Karaca E, Uçar M, Ateþ E, Yücel C, Ýlbey YÖ. Comparison of uroflowmetry tests performed with a sensation of normal desire to void versus urgency and correlation of test results with IPSS. Turkish Journal of Urology. 2020;46(5):378. DOI: 10.5152/tud.2020.20049 24.
Güven EO, Selvi I, Karaismailoðlu E. Association between benign prostate enlargement-related storage and voiding symptoms and systolic blood pressure: a single-center cross-sectional study. Sao Paulo Medical Journal. 2020;137:446-53. DOI: 10.1590/1516-3180.2018.0543.R3.160919

23. Lepor H. Pathophysiology of lower urinary tract symptoms in the aging male population. Reviews in urology. 2005;7(Suppl 7):S3.

24. Li X, Pan J-h, Liu Q-g, He P, Song S-j, Jiang T, et al. Selective transurethral resection of the prostate combined with transurethral incision of the bladder neck for bladder outlet obstruction in patients with small volume benign prostate hyperplasia (BPH): a prospective randomized study. Plos One. 2013;8(5):e63227. DOI: 10.1371/journal.pone.0063227.

25. Ojewola R, Oridota E, Balogun O, Alabi T, Ajayi A, Olajide T, et al. Prevalence of clinical benign prostatic hyperplasia amongst community-dwelling men in a South-Western Nigerian rural setting: A cross-sectional study. African Journal of Urology. 2017;23(2):109-15 https://doi.org/10.1016 /j.afju.2016.02.004

Original Article **Open Access**

The Effectiveness of Submucosal Dexamethasone after Third Molar Extraction. A Single Blind Randomized Clinical Trial

Saeed Ullah Shah, Nameera Agha, Abhishek Lal, Rahima Yousofi, Resham Nadeem, Naseer Ahmed

ABSTRACT:

Objective: To evaluate the efficacy of dexamethasone in alleviating pain and trismus of the patients who underwent extraction of the third molars.

Methodology: A total of 120 patients took part in this randomized, controlled trial. The wisdom teeth of patients were surgically extracted under local anesthesia. The patients were randomly assigned to one of two group and study control with 60 patients in each group. Preoperative and Postoperative measurements of edema, trismus and pain were analyzed. In study group, dexamethasone was immediately given after extraction. However, in control group, no dexamethasone was given to the patients. The paired t-test was carried out to compare the means scores of pains and trismus and. A p value of = 0.05 was judged significant.

Results: The pain scores of patients in group 1 were mostly pain-free on the third post-operative day after dexamethasone administration, with complete pain resolution in all patients on the seventh post-operative day. About trismus in post operative phase almost all of the patients belonging to group 1 did not report to suffer from trismus with just two patients complaining of mild trismus. Whereas, on the 7th post-operative day, all of the group 1 patients free from trismus. About the comparison of trismus, pain and Edema in study groups, a significant difference $p<0.05$ was found.

Conclusion: Inflammatory complications are frequently associated in the post operative phase of extraction of third molars. Dexamethasone has been proven to be useful in reduction of pain, trismus and edema experienced by the patients when no intervention has been given.

Keywords: Dexamethasone, Dental pain, Exodontia, Edema Postoperative complication, Trismus,

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INTRODUCTION:

The third molar root forms between the ages of 18 and 25, and it is the last tooth to erupt. However, it may continue to erupt even after the age of 25. The most common dentoalveolar procedure in oral and maxillofacial surgery is the removal of maxillary and mandibular third molars. Impaction being the most common reason and surgical procedure for removal of the third molar and is also associated with various postoperative complications such as permanent nerve damage Because impacted mandibular third molars are near to inferior alveolar vessels, surgical procedures to this highly vascular area result in exudate liberation, causing significant edema, discomfort, and trismus in the days following surgery and serious infection are the most severe complication of following molar extraction.[1] The factors contributing to these postoperative difficulties are related to the inflammatory process. Inflammatory symptoms differ from patient to patient in occurrence and its severity. Other causes include pericoronitis, cystic lesions, neoplasms, pathological, and root resorption which can cause detrimental effects on the tooth associated along with the neighboring teeth.[2,3]

Corticosteroids have been used at different dosages to lessen the inflammatory effects of third molar surgical removal.[4] Corticosteroids are available of its potential anti-inflammatory effects, dexamethasone is useful in decreasing pain and is

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currently the most dominant anti-inflammatory drug, with a long half-life.[5] Administered through intravenous or intramuscular route, betamethasone**,** dexamethasone, and methylprednisolone, are the most widely used corticosteroids.[6]

For the patients the administration of dexamethasone for the reduction of pain, trismus. However, duration and dosage should be kept in mind as prolonged use of corticosteroids can delay in the healing process and increase the patient's susceptibility to infections.[7]

A single glucocorticoid dose inhibits the synthesis and/or release of pro-inflammatory and inflammatory mediators in a variety of surgical procedures, with a reduction of fluid transudation and therefore edema.[8,9] In order to evaluate the use of dexamethasone to alleviate pain and trismus in patients underdoing extraction of third molars, various clinical trials have been carried out. They were given 4 mg of dexamethasone and postoperative pain was evaluated using a visual analog scale (VAS) and the degree of swelling was evaluated through facial reference points' variation. These assessments were obtained before the operation and after the surgery. The usefulness of dexamethasone in the reduction of pain and trismus has been reported in various clinical trials in the literature.[10,11]

Since the development of pain and trismus in patients who have undergone extraction of third molars can be proven to be troublesome for the patients, interventions are required to relieve the patients of such inflammatory complications. In this study, we aimed to evaluate the efficacy of dexamethasone in alleviating pain, trismus and edema of the patients who underwent extraction of the third molars.

METHODOLOGY:

In this study, the ethical approval was granted from the ethics and review committee of Altamash Institute of Dental Medicine, Pakistan (reference code: AIDM/ERC/07/2021/01). This study was conducted in accordance with the Declaration of Helsinki. The participants for this study were recruited using a convenience sample method.

In this randomized controlled trial, a total of 120 patients participated in which the bony impacted teeth (Third Molar) were surgically extracted under local anesthesia, after effectiveness of local anesthesia incision was given raised the mucosal periosteal flap expose the bone at buccal surface of teeth and buccal guttering of bone done to make a purchase point and then teeth section accordingly for ease of extraction. The patients who were diagnosed and advised surgical extraction of the third molars under local anesthesia with no co-morbidities were included in this study. Patients who had pericoronitis/infection at the time of surgery were unable to give informed consent, knew they had a hypersensitivity or allergic reaction to corticosteroids and had a recent history of taking anti-inflammatory, antibiotic, or narcotic drugs, lactating and smokers were excluded from the study. All the patients were selected from the Department of Oral and Maxillofacial Surgery, Altamash Institute of Dental medicine and to ensure voluntary participation, written informed consent was obtained from all participants after they were given full written and verbal information of the trial for publication of the study findings. The data that was collected from the participants was kept confidential throughout the study.

The patients were randomly divided into two groups, the Study group and Control with 60 patients in each group and the duration of the study were 6 months.

In the study group, each patient had rinsed with 5ml chlorhexidine mouth wash for a minute and the lingual nerve were blocked with local anesthesia (lidocaine 2% & epinephrine 1:10,0000) to proceed with the extraction after the procedure a dexamethasone with the dose of 4mg was immediately given to the patient buccally to the third molar extraction site as a submucosal injection. Post-operatively all the patients were prescribed with antibiotics and painkillers However, in the control group, each patient had rinsed with 5ml chlorhexidine mouth wash for a minute and the lingual nerve were blocked with local anesthesia (lidocaine 2% & epinephrine 1:10,0000) to proceed with the extraction after the procedure no dexamethasone was given to the group of patients. A toss and coin technique were used to divide patients into these groups**,** figure 1. It was a single-blinded technique.

All the standard surgical and aseptic measures were strictly followed. The surgeons who performed the surgery followed personal protective equipment to ensure aseptic measures.

The trismus, swelling and pain sequelae were assessed on the 3rd and 7th day of the extraction. The trismus were evaluated by using Varnier caliper scale with reference point of inter incisal distance less than 35mm interincisal distance consider trismus. swelling was measured by drawing two imaginary line one from outer cantus of eye into antigonion notch of mandible, 2nd line draw from tragus of ear to ala of the nose the interacting of two line make triangle through which we measure the swelling and pain was assess by using visual analog scale 1-3 mild, 4-6 moderate, 7-10 severe.

For data analysis of this study, we used Statistical Package for Social Sciences (SPSS) version 25. The descriptive analysis was carried out to calculate the percentage, mean and standard deviation of age, gender, type of impaction, pain, and trismus scores. The paired T-test was carried out to compare the means scores of pains and trismus in between the study group and control group. A p-value of =0.05 was considered to be as statistically significant.

RESULTS:

In this randomized controlled trial, we recruited a total of 120 patients. The patients were then randomized into 2 groups: Group 1 was administered Dexamethasone and Group 2 was control. The mean age of patients in the two

groups is as follows: Group 1: 28.55 ± 4.48 and Group 2: 29.28 ± 4.00. About gender, the distribution of males and females in each of the groups is as follows: Group 1: 24 and 36, and Group 2: 16 and 44. Regarding smoking, there were 17 smokers in group 1 and 9 smokers in group 2. The distribution of the type of impaction is presented in **t**able 1. About the pain scores of patients in group 1, most of the patients were pain free on the 3rd post operative day after the administration of dexamethasone, with complete resolution of pain in all of the patients on the 7th post operative day. However, patients in group 2 did experience mild pain, with some patients suffering from moderate and severe pain. Furthermore, most of the patients in group 2 on the 7th post operative day were pain free. About comparison of pain scores between the two groups, a significant difference was found (p-value= 0.001) as presented in table 2. About trismus in post operative phase almost all of the patients belonging to group 1 did not report to suffer from trismus with just two patients complaining of mild trismus. On the 7th post operative day, all of the group 1 patients free from trismus. However, majority of the patients of group 2 did not complaint of trismus, but few did complaint of experience mild to moderate trismus on the 3rd post operative day. Furthermore, on the 7th post operative day, patients belonging to group 2 did not experience any trismus. About the comparison of trismus amongst the patients, a significant difference was found (p-value= 0.004), as presented in table 3.

DISCUSSION:

The third molar teeth are the last to erupt with a relatively high chance of becoming impacted. Many causes are associated that requires the extraction of the third molars that includes impaction being the most frequent complaint of the patient and the surgical extraction of many impacted mandibular third molars which have been asymptomatic for years are often carried out to prevent the development of any future complications and pathologic conditions followed by caries, periodontitis and trauma. The third molars can be extracted either non-surgically or surgically, which varies from patient to patient. Complications associated with the removal of impacted teeth are relevant and are aided by local and general factors which include tooth position, age

Figure 1: Consort flow diagram of the study

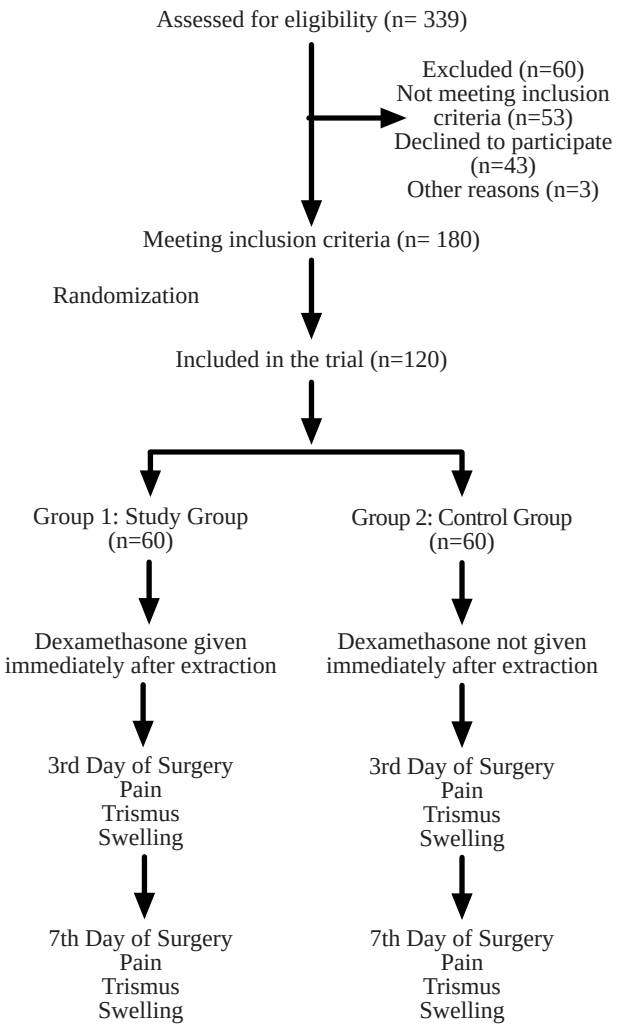

Table 1. Type of Impaction of Third Molar in the patients

	Type of Impaction			
Groups	Horizontal	Vertical	Mesioangular	Distoangular
Group 1	16 (26.66%)	11 (18.33%)	21 (12.25%)	12 (20%)
Group 2	14 (23.33%)	15 (25%)	17 (28.33%)	14 (23.33%)

Table 2. Comparison of pain scores in the patients (n=120)

Groups		Mean	N	Std. Deviation	Std. Error Mean	T	df	p-value
Study and Control groups	Group 1	3.85	60	0.659	0.085	5.958	59	0.001
	Group 2	3.06	60	0.936	0.120			

Table 3: Comparison of trismus in the patients

Groups		Mean	N	Std. Deviation	Std. Error Mean	T	df	p-value
Study and Control groups	Group 1	3.85	60	0.661	0.085	3.037	59	0.004
	Group 2	3.55	60	0.804	0.102			

of the patient, health status, knowledge and experience of the dental surgeon, and surgical equipment used. Complications associated with the removal of the third molar include damage of the sensory nerve leading to paresthesia, dry socket, infection, severe trismus, oro-antral fistula, buccal fat herniations. About surgical extraction of the third molars, pain and trismus is a frequent complaint experienced by the patients.

Glucocorticoids are known to have an anti-inflammatory that is documented well in the literature with the purposed mechanism that involves the suppression of accumulation of leucocytes and macrophages at the site of inflammation and preventing the formation of prostaglandins.[12] Corticosteroids act by suppressing each phase of the initial inflammatory response, thereby decreasing cellular permeability and capillary dilatation by inhibiting the production of vasoactive substances and diminishing the amount of cytokines. Furthermore, the generation of prostaglandin is repressed by corticosteroids, resulting in an analgesic effect. Corticosteroids have been proven to be useful in reducing pain and swelling experienced by the patients regardless of the route of administration. Dexamethasone is a corticosteroid, that is given as orally, intravenously, intramuscularly, and submucosal either in preoperative or post-operative phase.[13,14,7]

In this study, patients in group 1 were assigned to intra oral injections of administration of dexamethasone. On the 3rd post-operative day, most of the patients who were given dexamethasone were pain free with complete resolution of pain in the remaining patients on the 7th post operative day. These results correspond to various studies in the literature that concludes dexamethasone to alleviate pain after patients underwent extraction of the third molars.[15,5]

Trismus is a condition that is defined as limitation of mouth opening, a decrease in maximum interincisal opening that is a consequence due to edema, swelling, and pain cause by patient undergoing a surgical procedure. In this study, when comparison was done amongst the groups with respect to post-operative trismus, the results were found to be statistically significant. The patients who were assigned to dexamethasone, majority of the patients did not complaint of suffering limitation of mouth opening, with complete resolution of trismus on the 7th post operative day. These findings have also been reported in the studies in the literature that found dexamethasone to be useful in preventing trismus in patients who underwent third molar extractions.[16,17]

About the patients who were not assigned to any intervention in the post operative phase of the third molar extraction, these patients did experience mild to moderate levels of pain and trismus. These results correspond with a study by Ngeow et al that reported higher level of pain scores in patients that were not assigned to any pain reduction intervention [18]. However, a study by Grossi et al found no difference between the control and dexamethasone groups in reduction of pain scores, swelling, and trismus.[19]

Smoking is known to interfere with the healing process after third molar extraction. Most of the times, the patients are instructed to discontinue smoking for a certain period of time. Smoking may disrupt the formation of blood clot in the socket and hinder the normal healing process of the socket, that eventually delay the healing of the socket.[20] Moreover, smoking also has an effect on the levels of pain as smokers tend to experience greater levels of postoperative extraction pain as compared to the non-smokers.[21]

Different studies have been carried to evaluate its effectiveness in controlling pain, trismus and swelling. Studies do suggest that dexamethasone is effective in reducing pain, swelling, and trismus complaint of the patients.[22] Moreover, in a study by Latt et al, it was concluded that dexamethasone injection in the pterygomandibular space effectively reduced the postoperative pain and its sequelae after lower mandibular third molar extractions.[23]

As the inflammation progress the intestitial fluid accumulation due to transudation from injured blood vessels and obstruction of lymphatic drainage by fibrin and fibrinogen clots derived from plasma and adjacent injured vessels leads to postoperative edema complications experienced by the patients in the post operative phase of third molar extractions is a bothersome experience for the patients that mandates intervention for its resolution. Despite the strengths of this study such as inclusion of large sample size of the patients, and regular follow up of the patients, we were met with some limitation. Firstly, compliance of the patients with the drugs might be a factor that might affect the results of this study. Lastly, patients were advised for temporary cessation of smoking which the patients might not have followed.

CONCLUSION:

The post operative phase complications are frequently associated with the extraction of third molars. Dexamethasone has been proven to be useful in reduction of pain, swelling and trismus experienced by the patients when no intervention has been given. Thus, we recommend the submucosal administration of dexamethasone, as an easier and more comfortable route of administration which showed significant difference in reduction in pain, swelling and trismus, and on entire assessment it was found superior for the improvement of postoperative quality of life of patient.

Authors Contribution:
Saeed Ullah Shah: Conceived and designed
Nameera Agha: Collected data
Abhishek Lal: Analysis
Rahima: Interpretation of Data
Resham Nadeem: Wrote the paper
Naseer Ahmed: Performed the Analysis

REFERENCES:

1. Santosh P. Impacted mandibular third molars: Review of literature and a proposal of a combined clinical and radiological classification. Ann Med Health Sci Res [Internet].2015; 5(4):229. https://doi.org/10.4103/2141-9248.160177
2. Patil S, Halgatti V, Khandelwal S, Santosh BS, Maheshwari S. Prevalence of cysts and tumors around the retained and unerupted third molars in the Indian population. J Oral Biol Craniofacial Res [Internet]. 2014 ;4(2):82–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2212426814000335
3. Mello FW, Melo G, Kammer PV, Speight PM, Rivero ERC. Prevalence of odontogenic cysts and tumors associated with impacted third molars: A systematic review and meta-analysis. J Cranio-Maxillofacial Surg [Internet]. 2019 Jun;47(6): 9961002. https://doi.org/10.1016/j.jcms.2019.03.026
4. Sugragan C, Sirintawat N, Kiattavornchareon S, Khoo LK, KC K, Wongsirichat N. Do corticosteroids reduce postoperative pain following third molar intervention? J Dent Anesth Pain Med [Internet]. 2020;20(5):281. https://jdapm. org/DOIx. php? id= 10.17245/jdapm. 2020. 20.5.2 81
5. O'Hare PE, Wilson BJ, Loga MG, Ariyawardana A. Effect of submucosal dexamethasone injections in the prevention of postoperative pain, trismus, and oedema associated with mandibular third molar surgery: a systematic review and meta-analysis. International journal of oral and maxillofacial surgery. 2019;48(11):1456-69
6. Hodgens A, Sharman T. Corticosteroids [Internet]. StatPearls. 2021. Available from: . nih.gov/ pubmed/ 32119499
7. Arora SS, Phull T, Kumar I, Kumar A, Kumar N, Singh H. A comparative study of the effect of two dosages of submucosal injection of dexamethasone on postoperative discomfort after third molar surgery: a prospective randomized study. Oral and maxillofacial surgery. 2018 Jun;22(2):225-30.
8. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol [Internet]. 2011 ;335(1):2–13. https://doi.org/10.1016/j.mce. 2010.04.005
9. Yasir M, Goyal A, Bansal P, Sonthalia S. Corticosteroid Adverse Effects [Internet]. StatPearls. 2021. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30285357
10. Sreesha S, Ummar M, Sooraj S, Aslam S, Roshni A, Jabir K. Postoperative pain, edema and trismus following third molar surgery – A comparitive study between submucosal and intravenous dexamethasone. J Fam Med Prim Care [Internet]. 2020;9(5):2454. Availablefrom: https://journals.lww. com/jfmpc/Fulltext/ 2020/09050/ Postoperative_ pain,_edema_ and_trismus_ following.57.aspx
11. Bamgbose BO, Akinwande JA, Adeyemo WL, Ladeinde AL, Arotiba GT, Ogunlewe MO. Effects of co-administered dexamethasone and diclofenac potassium on pain, swelling and trismus following third molar surgery. Head Face Med [Internet]. 2005 ;1(1):11. Available from: https://head-face-med.biomedcentral. com/articles/10.1186/1746-160X-1-11
12. Ricciotti E, FitzGerald GA. Prostaglandins and Inflammation. Arterioscler Thromb Vasc Biol [Internet]. 2011 ;31(5) :986–1000. https://doi.org/10.1161/ ATVBAHA.110. 207449
13. Antunes AA, Avelar RL, Martins Neto EC, Frota R, Dias E. Effect of two routes of administration of dexamethasone on pain, edema, and trismus in impacted lower third molar surgery. Oral Maxillofac Surg [Internet]. 2011 ;15(4):217–23. Available from: http://link.springer.com/10.1007/s10006-011-0290-9
14. Gholami M, Anbiaee N, Abad SB, Asadi M. What Are the Effects of Methylprednisolone Injection Into the Masseter and Gluteal Muscle on Pain, Edema, and Trismus After Impacted Lower Third Molar Surgery? A Randomized Clinical Trial. Journal of Oral and Maxillofacial Surgery. 2021 Sep 1;79(9):1829-36.
15. Falci SGM, Lima TC, Martins CC, Santos CRR dos, Pinheiro MLP. Preemptive Effect of Dexamethasone in Third-Molar Surgery: A Meta-Analysis. Anesth Prog [Internet]. 2017 Sep 1;64(3):136–43. https://doi.org/10.2344/anpr-64-05-08
16. Lima CAA, Favarini VT, Torres AM, da Silva RA, Sato FRL. Oral dexamethasone decreases postoperative pain, swelling, and trismus more than diclofenac following third molar removal: a randomized controlled clinical trial. Oral Maxillofac Surg [Internet]. 2017;21(3):321–6. Available from: http://link.springer.com/10.1007/s10006-017-0635-0
17. Sabhlok S. Randomized Controlled Trial to Evaluate the Efficacy of Oral Dexamethasone and Intramuscular Dexamethasone in Mandibular Third Molar Surgeries. J Clin DIAGNOSTIC Res [Internet]. 2015;DOI : 10.7860/JCDR/2015 /13930.6813
18. Ngeow WC, Lim D. Do Corticosteroids Still Have a Role in the Management of Third Molar Surgery? Adv Ther [Internet]. 2016;33(7):1105–39. Available from: http://link.springer. com/10.1007/s12325-016-0357-y
19. Grossi GB, Maiorana C, Garramone RA, Borgonovo A, Beretta M, Farronato D, et al. Effect of Submucosal Injection of Dexamethasone on Postoperative Discomfort After Third Molar Surgery: A Prospective Study. J Oral Maxillofac Surg [Internet]. 2007;65(11):2218–26. Availablefrom: https://linkinghub.elsevier.com/retrieve/pii/S0278239106022051
20. Sanari AA, Alsolami BA, Abdel-Alim HM, Al-Ghamdi MY, Meisha DE. Effect of smoking on patient-reported postoperative complications following minor oral surgical procedures. Saudi Dent J [Internet]. 2020;32(7):357–63. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1013905219306339
21. Al-Delayme RM. The effect of cigarette smoking on the severity of pain, swelling and trismus after the surgical extraction of impacted mandibular third molar. J Clin Exp Dent. 2013;5(3):e117-21. DOI: 10.4317/jced.50979
22. Falci SGM, Lima TC, Martins CC, Santos CRR dos, Pinheiro MLP. Preemptive Effect of Dexamethasone in Third-Molar Surgery: A Meta-Analysis. Anesth Prog [Internet]. 2017 ;64(3):136–43. Available from: https://meridian.allenpress.com/anesthesia-progress/article/64/3/136/25009/Preemptive-Effect-of-Dexamethasone-in-ThirdMolar
23. Latt MM, Kiattavorncharoen S, Boonsiriseth K, Pairuchvej V, Wongsirichat N. The efficacy of dexamethasone injection on postoperative pain in lower third molar surgery. J Dent Anesth Pain Med [Internet]. 2016;16(2):95. Available from: https://jdapm.org/DOIx.php?id=10.17245/jdapm.2016.16.2.95

Original Article **Open Access**

Frequency and Determinants of Postpartum Depression among Mothers Living in Karachi

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ABSTRACT

Objective: To determine the frequency of Postpartum Depression (PPD) among mothers living in Karachi and to find out the determinants of predispose mothers to Postpartum Depression.

Study Design and Setting: The study was cross sectional analytical and was carried by online survey of mothers living in Karachi

Methodology: Total duration was six months from 1st January, 2020 to 31st July, 2020. The calculated sample size of study was 369. The study was approved by the Ethical Review Committee of Bahria University Health Sciences Campus, Karachi. Random sampling technique was used to recruit subjects. 294 participants were part of the research. Mothers with previous history of depression and those who had given birth to healthy babies were included in the study. Mothers who have had miscarriage or pre-mature babies were excluded. Questionnaires in both English and Urdu languages were used for the research. PPD was assessed by the help of Edinburgh Post Natal Depression Scale (EPDS). The score of greater than 12 was considered to be indicative of PPD.

Results: A total of 294 mothers were enrolled in the study, 187 mothers had an EPDS score >12 giving prevalence of PPD as 63.6%. This study showed that mothers with PPD were more likely not to breastfeed their child (p=0.01), had lack of family support (p=0.00) and had previous history of depression as well (p=0.00).

Conclusion: The present study concluded that frequency of postpartum depression was 63.6%. Lack of breastfeeding, previous history of depression and lack of family support were among the determinants that predispose mothers to postpartum depression.

Key words: Postpartum, depression, determinants, mothers

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INTRODUCTION:

Postpartum depression is a type of mood related disorder that is manifested within three months after the child's birth. There appears weakening of bond between the mother and the child along with ego-dystonic thoughts. The depressive thoughts can lead to a mother harming a child and even end up killing her own baby.[1] Depression, anxiety, multiple pregnancies are considered to be important risk factors. Lack of breast feeding and absence of care towards the mother by the spouse are also considered as vital social factors contributing to the disorder along with low socioeconomic status and smoking history.[2,3] Life style factors include decrease physical exercise, food low in healthy nutrients along with disturbed sleep pattern.[2] Azad et al in their study have identified several factors including unintentional pregnancy, job work after child birth, loss of job due to pregnancy, past history of still born child, miscarriage, death of the child, poor marital life relationship, violence from the spouse, low socioeconomic status and unintended pregnancy as the causes leading to PPD.[4]

The prevalence of postpartum depression in adult mothers range in between 10% to 15%. Anokye reported the prevalence to be 7% in Ghana population.[5] A study conducted in Turkey found overall prevalence to be 23.8% with 21.2% rate in the developed cities as compared to 25% prevalence

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in the developing cities.[3] A research study carried in Dhaka, Bangladesh has documented the prevalence to be 39.4% within first year of delivering a child. On an average out of every 100 women, 40 were declared as having PPD.[4] Postpartum disorder is commonly seen illness among the females of Pakistan. The prevalence rate is variable and ranges in between 28% to 63%. Several factors contribute to the development of PPD in Pakistan, including environmental, cultural and social factors.[6] A study conducted in Islamabad has documented the frequency of PPD to be 17.3%.[7]

Postpartum depression presents significant problems not only for mothers but also for children. A recent study has mentioned that the after effects of the disorder can even lead to infanticide and suicide.[8] The general public lacks awareness and that is the reason behind the neglect given to this disorder.[9] PPD is considered to be among the illnesses which are given high priority by the public health.[10] Despite of various treatment options, females living in Pakistan are not treated.[8] This disorder should be treated as it can lead to disturbing bond between the mother and the child along with several psychosocial issues in the child.[1] Among the treatment options, psychosocial support is considered to be among the most effective ones.[5] Effective treatment modalities should take into account the cultural aspects and the cost of treatment.[4]

There are several studies on postpartum depression that have been predominantly conducted in western societies. The lack of research on postpartum depression in developing countries like Pakistan could lead to a gap in assessing the global burden of disease. Therefore the study was planned with the objectives of determining the frequency of postpartum depression and its determinants that predispose the mothers to PPD. The findings of this study will help to fill the gaps in the literature about PPD in Pakistan and along with that it can help decision makers to ensure better planning, resource allocation and delivery of health services.

METHODOLOGY:

The present research was a cross-sectional study. The study was approved by the Ethical Review Committee of Bahria University Health Sciences Campus, Karachi (ERC number is 45/2020). It was carried out through online survey. The sample size for this study was calculated from StatCalc sample size calculator tool with 95% confidence level and 5% margin of error. The calculated sample size of the study was 369. Before the start of survey, consent was taken from all the participants. Total number of responses received was 446 and finally the valid number of responses among these was 294. Random sampling technique was applied and each respondent was given equal chance of selection. All mothers including first time mothers, mothers with previous history of depression and have given birth to healthy babies were included in the study. Mothers who have had miscarriage or pre-mature babies were excluded from the study. The web-link of the survey questionnaire was shared by the help of text-based instant messaging (WhatsApp). The study was conducted through a period of 7 months (1 January, 2020 to 31st July, 2020). The recruited participants were then identified as suffering from PPD and also the determinants associated with Postpartum Depression (PPD) were noted.

Since, this was an online research therefore questionnaire was constructed through a software called Surveylegend. It consisted of a set of 10 questions from Edinburgh Postnatal Depression Scale (EPDS) This is a self-rating scale, which is used to screen mothers for postpartum depression. When the scores were greater than 12, they were considered having postpartum depression (PPD). Another set of custom designed questions regarding sociodemographic, obstetrics and newborn variables were asked to identify the determinants associated with postpartum depression. All the material had been translated into local language Urdu for the convenience of the online participants.

Data was received in the form of excel spreadsheet, was entered and analyzed by using Statistical Package for Social Sciences (SPSS), version 26. Analysis was carried through descriptive statistics to calculate the frequency and percentages of main variables like age, qualification, working status, parity, delivery type, infant gender, feeding status, and family support, previous history of depression and awareness of PPD. Multi-variable analysis was done using the Chi-Square test to compare the women with and without PPD with all sociodemographic, obstetric and medical variables. The results were considered as significant when p value was =0.05.

RESULTS:

Out of the total 294 participants, majority were found to be suffering from postpartum depression based on the EPDS score (Figure-1). The mean of depression score turns out to be 14.4±6.1. This study showed that mothers with PPD and those without it differed in terms of breast feeding their children, support of family and previous history of depression (Table 1). The females differ in terms of awareness about the postpartum depression. (Figure 2)

Figure 1: Pie chart showing prevalence of depression in the sample based on EPDS score

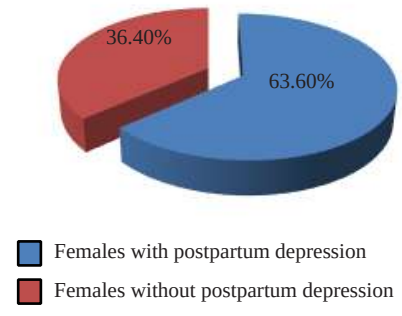
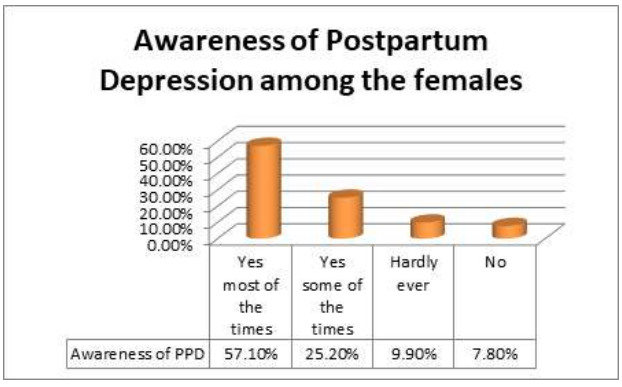


Table 1: Comparison of study variables with postpartum depression verses no depression

Variables	Women with PPD (N=187)	Women without PPD (N=187)	P Value
	N (%)	N (%)	
Age			
Less than 20 years	03 (1.6%)	01 (0.9%)	0.415
20-30 years	134 (71.6%)	71 (66.3%)	
30-40 years	40 (21.3%)	24 (22.4%)	
More than 40 years	10 (5.3%)	11 (10.2%)	
Qualification			
Primary	10 (5.3%)	08 (7.4%)	0.848
Secondary	01 (0.5%)	00 (0%)	
Matric	10 (5.3%)	05 (4.6%)	
Intermediate	23 (12.2%)	20 (18.6%)	
Bachelors	116 (62%)	62 (57.9)	
Postgraduate	27 (14.4%)	12 (11.2%)	
Working status			
Housewife	135 (72.1%)	85 (79.4%)	0.168
Working women	52 (27.8%)	22 (20.5)	
Parity			
Primiparous	100 (53.4%)	47 (43.9%)	0.185
Multipara	87 (46.5%)	60 (56.0)	
Delivery Type			
Complicated	75 (40.1%)	37 (34.5%)	0.348
Un-complicated	112 (59.8%)	70 (65.4%)	
Feeding Status			
Mother milk	116 (62%)	81 (75.7%)	**0.01***
Formula milk	71 (37.9%)	26 (24.2%)	
Family support			
Yes, most of the time	98 (52.4%)	88 (82.4%)	**0.00***
Yes, some of the time	60 (32.0%)	11 (10.2%)	
Hardly ever	20 (10.6%)	05 (2.6%)	
No	09 (4.8%)	03 (1.6%)	
Previous history of depression			
Yes, Most of the time	46 (24.5%)	03 (2.8%)	**0.00***
Yes, some of the time	81 (43.3%)	18 (16.8%)	
Hardly ever	30 (16%)	26 (24.2%)	
No	30 (16%)	60 (56%)	

Figure 2 Demographic characteristics of enrolled participants



DISCUSSION:

PPD is included among the mood disorders that affects ten to fifteen percent of mothers on yearly basis[5] and is seen among the females belonging to different social status around the globe.[3,4] The current study explored the prevalence of postpartum depression in females in our local setup and tried to identify associated factors which may predispose or perpetuate the disorder. In this study, the prevalence of postpartum depression among mothers of Pakistan is n=187 (63.6%) out of total participants 394. Analogous results were stated by a study carried in Peshawar mentioning the prevalence to be 62.7%.[9] The percentage of prevalence is considerably high as compared to studies conducted in various regions of our country. A research conducted at Islamabad has reported the prevalence to be 17.3%.[7] A longitudinal study in Pakistan reported the mean PPD score of 11.18 while a study conducted by Aliani R et al reported the prevalence to be 12.5%.[11,8] Postpartum depression has been seen to be affected by differences in ethical backgrounds.[12]

Although the illness exists both in the western societies and the eastern ones, the difference lies in the etiological factors.[13] There are various etiological factors that lead to the mental ailment of PPD. Previous history of depression is among the factors that are associated with a higher risk of postpartum depression. The second most important finding of our research is that mothers who have depression prior to conception are more susceptible to postpartum depression. Various studies have mentioned the relationship between postpartum depression and previous history of depression. Tariq et al in their study have documented the relation between antenatal and post natal depression.[11] A study conducted in Sweden have documented that females with history of depression have twenty times more chances of developing postpartum depression than those without the positive history of depression.[14] An Egyptian research with 33.5% of PPD prevalence has also mentioned the linkage between onset of the postpartum depression and previous depression history.[15] This suggests that postpartum depression is strongly linked to previous episodes of depression.

The result of the current study showed that those mothers who are not breastfeeding their children are likely to develop postpartum depression. A study conducted on Latino females have also documented parallel results stating that postpartum depression is correlated with cessation of breast feeding.[16] Other studies conducted in United States of America and Korea have also mentioned similar results mentioning the linkage between lack of breast feeding and development of PPD.[17,18] This signifies the protective physiological effects of breast milk in prevention of PPD.

Societal factors play a major role in the development of postpartum depression. Third important variable in the current research is family support. According to our results,

those mothers who have had lack of family support also suffer from postpartum depression. Other studies have shown significant association between the occurrence of postpartum depression and absence of family support. Another study conducted in Pakistan has also highlighted the link between high social support and prevention of PPD.[2] Studies conducted in Hazara, Rawalpindi and Islamabad have also documented the protective supportive role of family towards prevention of PPD. Those females who live in a nuclear setup are more prone to develop PPD as compared to those who live in joint family system setup.[19,20] A study in India has also thrown light on the impact of societal factors in contributing towards the females developing postpartum depression. The social setup does not allow women to seek medical advice on time. Disorders like PPD is seen as a stigmatizing event in the lives of the mothers.[13] A Japanese research has documented that the family members living with the pregnant mother are among factors that can affect the development of PPD. Postpartum depression was reported more in those females who live with their in laws as compared to those who live with their spouses and children only. Spouse support and economical support help in alleviating the symptoms.[21] Similarly, a study conducted in North Carolina has mentioned that effects of social support play an instrumental role in the prevention of development of PPD.[22] A recent study conducted in Taiwan has also endorsed the positive outcomes of psychosocial support. The study stated that first time mothers can be aided by providing family support and midwifery provision in order to cater the needs of the mothers.[23] A study conducted in France has highlighted that positive support from the spouse can nullify the effects of inequalities from the surrounding members towards the mother and hence play a vital role in combatting postpartum depression.[24] Ambrosini et al in their article have highlighted the contribution of cultural norms in facilitating the occurrence and progress of PPD.[25] Support from the family is shown to be an essential component in PPD occurrence.

The current study has few limitations. The study was conducted at a single center. Multi-centered studies would have enabled us to generalize the results. Secondly the participants were recruited from hospital setup that is why the sample is not representative of population.

Further studies with longitudinal study design could be beneficial in acquiring a follow up feedback from the patients. In future, studies with variable ethnic population should be planned to determine the effects of ethnicity on PPD.

CONCLUSION:

The present study concluded that frequency of postpartum depression was 63.6%. Lack of breastfeeding, previous history of depression and lack of family support were among the determinants that predispose mothers to postpartum depression.

Authors Contribution:
Fareeha Shahid: Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data
Quratulain Javaid: Manuscript writing, revising the article, final approval of version
Umama Shakeel Ahmed: Substantial contributions to conception, design and acquisition of data
Fatima Farooq: Substantial contributions to conception, design and acquisition of data
Neelam Kumari: Substantial contributions to conception, design and acquisition of data
Qalandar Shah: Substantial contributions to conception, design and acquisition of data

REFERENCES:

1. Siedlecka D, Wróbel-Knybel P, Krzewicka-Romaniuk E, Mica³ W, Skoczyñski M. Postpartum depression–a mood disorder after delivery. J Educ Health Sport. 2019;9(9):1124-1130. DOI http://dx.doi.org/10.5281/zenodo.3464246
2. Ghaedrahmati M, Kazemi A, Kheirabadi G, Ebrahimi A, Bahrami M. Postpartum depression risk factors: A narrative review. J Educ Health Promot. 2017;6:1-24. DOI: 10.4103/jehp.jehp_9_16
3. Ozcan NK, Boyacýoglu NE, Dinç H. Postpartum depression prevalence and risk factors in Turkey: a systematic review and meta-analysis. Arch Psychiatr Nurs.2017;31(4):420-428. https://doi.org/10.1186/s12884-021-04016-9
4. Azad R, Fahmi R, Shrestha S, Joshi H, Hasan M, Khan AN, Chowdhury MA, Arifeen SE, Billah SM. Prevalence and risk factors of postpartum depression within one year after birth in urban slums of Dhaka, Bangladesh. PloS one. 2019;14(5): e0215735. https://doi.org/10.3390/ijerph17134727
5. Anokye R, Acheampong E, Budu-Ainooson A, Obeng EI, Akwasi AG. Prevalence of postpartum depression and interventions utilized for its management. Ann Gen Psychiatry.2018;17(1):1-8. doi: 10.1186/s12991-019-0244-4
6. Gulamani SS, Shaikh K, Chagani J. Postpartum depression in Pakistan: a neglected issue. Nurs Womens Health. 2013; 17: 147-152. DOI: 10.1111/1751-486X.12024
7. Shah S, Lonergan B. Frequency of postpartum depression and its association with breastfeeding: A cross-sectional survey at immunization clinics in Islamabad, Pakistan. Pakistan. J Pak Med Assoc. 2017;67(8):1151-1156.
8. Aliani R, Khuwaja B. Epidemiology of postpartum depression in Pakistan: A review of literature. National Journal of Health Sciences. 2017;2(1):24-30.DO1: 10.21089/njhs.21.0024
9. Bakhtiar H, Khaliq MM, Nawaz A, Asif M, Jamil S, Jamal S, et al. Risk factors associated with postpartum depression in two tertiary care hospitals of Peshawar: a comparative cross-sectional study. J Rehman Med Inst. 2020;6(3):16-9.
10. Layton H, Bendo D, Amani B, Bieling PJ, Van Lieshout RJ. Public health nurses' experiences learning and delivering a group cognitive behavioral therapy intervention for postpartum depression. Public Health Nurs. 2020;37(6):863-70. DOI: 10.1111/phn.12807
11. Tariq N, Naeem H, Tariq A, Naseem S. Maternal depression and its correlates: A longitudinal study. J Pak Med Assoc. 2021;71(6):1618-1622. doi: 10.47391/JPMA.352.

12. Guintivano J, Sullivan PF, Stuebe AM, Penders T, Thorp J, Rubinow DR, Meltzer-Brody S. Adverse life events, psychiatric history, and biological predictors of postpartum depression in an ethnically diverse sample of postpartum women. Psychol Med. 2018;48(7):1190-200. doi: 10.1017/S0033291717002641

13. Kapoor DA. A Critical Analysis of the Biopsychosocial Risks Associated with Postpartum Depression in Indian Mothers. Inquiry. 2021;13(02):1-10.

14. Silverman ME, Reichenberg A, Savitz DA, Cnattingius S, Lichtenstein P, Hultman CM, Larsson H, Sandin S. The risk factors for postpartum depression: A population-based study. Depress Anxiety 2017;34(2):178-187. doi: 10.1002/da.22597

15. Ahmed GK, Elbeh K, Shams RM, Malek MA, Ibrahim AK. Prevalence and predictors of postpartum depression in Upper Egypt: A multicenter primary health care study. J Affect Disord. 2021;290:211-218. doi: 10.1016/j.jad.2021.04.046.

16. Lara-Cinisomo S, McKenney K, Di Florio A, Meltzer-Brody S. Associations between postpartum depression, breastfeeding, and oxytocin levels in Latina mothers. Breastfeed Med. 2017;12(7):436-442. doi: 10.1089/bfm.2016.0213.

17. Webber E, Benedict J. Postpartum depression: a multi-disciplinary approach to screening, management and breastfeeding support. Arch Psychiatr Nurs. 2019;33(3):284-289. doi: 10.1016/j.apnu.2019.01.008.

18. Nam JY, Choi Y, Kim J, Cho KH, Park EC. The synergistic effect of breastfeeding discontinuation and cesarean section delivery on postpartum depression: A nationwide population-based cohort study in Korea. J Affect Disord. 2017;218:53-58. doi: 10.1016/j.jad.2017.04.048.

19. Kazmi SF, Khan M, Tahir R, Dil S, Khan AM. Relationship between social support and postpartum depression. Ann Pak Inst Med Sci. 2013;9(4):191-194.

20. Sadiq G, Shahzad Z, Sadiq S. Prospective study on prevalence and risk factors of post natal depression in Rawalpindi/ Islamabad, Pakistan. Rawal Med J. 2016;41(1):64-7.

21. Honjo K, Kimura T, Baba S, Ikehara S, Kitano N, Sato T, et al. Association between family members and risk of postpartum depression in Japan: Does “who they live with” matter?-The Japan environment and Children's study. Soc Sci Med. 2018;217:65-72. doi: 10.3389/fpsyt.2021.736306

22. Pao C, Guintivano J, Santos H, Meltzer-Brody S. Postpartum depression and social support in a racially and ethnically diverse population of women. Arch Womens Ment Health. 2019;22(1):105-114. doi: 10.1007/s00737-018-0882-6.

23. Sangsawang B, Deoisres W, Hengudomsub P, Sangsawang N. Effectiveness of psychosocial support provided by midwives and family on preventing postpartum depression among first-time adolescent mothers at 3-month follow-up: A randomised controlled trial. J Clin Nurs. 2021;30(11-12):1-14. Doi: 10.1111/jocn.15928.

24. Nakamura A, Lesueur FE, Sutter-Dallay AL, Franck JÈ, Thierry X, Melchior M, van der Waerden J. The role of prenatal social support in social inequalities with regard to maternal postpartum depression according to migrant status. J Affect Disord. 2020;272:465-73.

25. Ambrosini A, Stanghellini G. Myths of motherhood. The role of culture in the development of postpartum depression. Ann Ist Super Sanita. 2012;48:277-86. doi: 10.4415/ ANN_12_03_08

Original Article **Open Access**

Magnetic Resonance Imaging of Lumbar Spine in Lower Backache: A Comparative Study on Gender Basis

Nazia Azeem, Muhammad Anwar, Shazia Kadri

ABSTRACT

Objective: To compare the clinical features of lower backache with Magnetic Resonance Imaging (MRI) findings on gender basis.

Study design & Setting: A cross-sectional descriptive study was carried out among male & female patients with a backache at Sir Syed Hospital, Karachi. This study conducted from 1st Jan 2020 to 1st June 2020. We studied 90 patients by using the non-probability convenient sampling technique.

Methodology: Lower backache is a common problem that creates disability. MRI lumbar spine without contrast were reviewed with clinical complaints. Performa was used after the ethical approval from Institutional Research and Ethical committee. Components focused during the study in MRI findings at different spinal levels were disc bulging, neural foraminal compromise, nerve root compression, ligamentum flavum and facet joint hypertrophy.

Results: The results showed that the mean age of 90 patients was 44.64 years. On MRI imaging 46(86.8%) males and 26(70.3%) females had disc desiccation but multi-level disc osteophyte complexes were demonstrated more in females 11(29.7%). Diffuse disc bulge is more in males at L4-5 and L5-S1 level 49(92.5%) than in females 34(91.9%) at L4-5 and 33(89.2%) at L5-S1 level with mild to moderate spinal canal stenosis. The narrowing of Neural foramen is almost similar at L4-5 level in both gender but more at L5-S1 in females 35(94.6%) as compared to males 49(92.5%) with nerve root compression. Overall male patients tended to have slightly more disc degenerative changes than females.

Conclusion: Lower Lumbar disc disease is a common problem showing significant disc space narrowing and bulges slightly more in our male population than females.

Keywords: Low back pain, lumbar radiculopathy, foraminal compression, Magnetic resonance Imaging

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INTRODUCTION:

The main function of vertebral column is to protect the spinal cord and acts as a support of the body. Lower back ache is a frequent cause of disability. From the Global Burden of Disease Study, it was observed that low back pain comes in a leading position in terms of disability and the chances of its occurrence is 9.4%.[1] Low back pain is a common of the column. It can resolve by itself with care without effecting the function. Sometimes it takes a longer duration to resolve. Chronic low backache is defined as pain that continues for 12 weeks or more. About 20% of people who are affected by acute low backache develop chronic pain with constant and continual symptoms for one year.[2]

The spine have five vertebral bodies (L1-L5) in the lumbar region and bears most of the weight of the upper part of body. Back pain can occur due to many reasons like occupational hazards, osteomyelitis (infection involving vertebrae), deficiency of vitamin D, obesity, age-related changes, postural imbalance, and pregnancy in women.[3,4] It was noted that One-third of nursing staff in Pakistan have lower back issues related to their occupation and 94% of the staff likes to take rest for the relief of symptoms.[5] The person's age determines the cause of the low back pain. The workers of ages between 30- 50 years are more affected by lower back pain. However, congenital abnormalities like Spina bifida having incomplete development of the cord can cause lower back pain (LBP). Sprains (overstretching of ligaments), strains (tears in tendons or muscle), and spasms (an abrupt contraction of a muscle) can also present as LBP. Any type of severe injury can compress the spine resulting in rupture of disc ultimately leading to LBP. Other causes include radiculopathy (in which compression of the sciatic nerve can occur), any tumor, or degenerative problems. Degenerative changes in the intervertebral disc led to

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detoriation of the facet joints.[6] The probability of wear and tear of disc usually increase with age and may not give rise to any symptoms, but with progression it can cause severe LBP. [7]

A comprehensive clinical history and physical examination can usually diagnose severity of illness that may be resulting in back pain.[8] There are investigations such as blood test, bone scan, and discography while imaging tests like computed tomography (CT) and Magnetic Resonance Imaging (MRI) are a more beneficial and are used for comparison between clinical manifestations in chronic low back pain (CLBP).[9] Magnetic resonance imaging (MRI) provides excellent detail of muscles, ligaments, tendons, infection/ inflammation, neoplastic mass, disc herniation or rupture, or nerve root compression.

MRI is an excellent modality in the neurological examination that provides best details of nerve root compression by more than one sequence of like T1WI and T2WI.[10] Different studies suggested that MRI has better sensitivity and reliability than other equipment and is more illustrative than computed tomography scan. It can reveal pathologies that are not obvious clinically. Acute back pain can be managed symptomatically. Medicines would be prescribed according to the appearance of symptoms. The other treatment option of chronic low back pain are thermotherapy, acupuncture, spinal mobilization, manipulation, back strengthening exercises. Thus, clinical findings of MRI in lower back pain decide either it would be treated by conservative or surgical interventions. The purpose of our study is to compare the clinical features of low backache based on MRI findings in the male and female gender.

METHODOLOGY:

This is a cross-sectional descriptive study through a non-probability convenient sampling technique. It was conducted at Sir Syed Hospital, situated in Karachi, Pakistan. The duration of the study was six months from 1st Jan 2020 to 1st June 2020. The sample size was calculated on the basis of the nationwide Swedish spine registry and the intended sample size was 90.

Data with a sample size of ninety patients were collected after approval from the ethical review board of Sir Syed Hospital (Approval # SSCMS04). Informed consent was taken from all patients included in the study.

The patients with a complaint of lower back pain, numbness of lower limbs, single or bilateral radiculopathy and clinical findings of MRI were included in the study. Ages of the patients were between 20 to 75. Patients with a history of accident, infection, neoplastic mass, metastasis and vascular pathology, or any severe surgical procedure of spine were excluded from the study. Performa was prepared after taking ethical approval and informed consent. This study was based on a comparison of gender either male or female. Symptoms of low backache involve numbness and unilateral or bilateral Radiculopathy in lower limbs. The duration of complaints usually varied from months, years or of unknown duration. MRI lumbar spine without contrast were reviewed especially Sagittal images were reviewed in both T1 and T2 sequence. Axial images in T2 sequence parallel to intervertebral disc whereas, sagittal images were of 4 mm slice thickness with 0.3 mm inter-slice gap. The scan was reviewed at the levels of L2- L3 to L5-S1 showing imaging features of narrowing of Neural Foramen and Lateral Recess, central canal narrowing, hypertrophy of ligamentum flavum and facet joints.

Statistical Package for Social Sciences (SPSS) version 21 used for data analysis. The mean, standard mean, and deviation for qualitative data and frequency and percentage for qualitative data calculated. Fischer Exact Test was applied to find the significance and to compare the conclusion of the clinical significance of MRI in both groups. A P value ≤ 0.05 was regarded as statistically significant.

RESULTS:

Our result shows 44.64 years as the mean age of 90 patients of our study in which 53 (58.9 %) were males (mean age - 44.45) and 37 (41.1 %) patients were females (mean age - 44.91). Most of the patients, 33 out of 90 (36.7%) complained of radiation of pain bilaterally in the lower limbs which is found more in females 14(37.8%) than males 19(35.8%) . However, extending pain to the right leg is more commonly seen (24.3 %) especially in females with variable durations, but with unknown duration 30(56.6%) in males with significant P value of 0.029. After reviewing MRI images, it was observed that individual patients showed variation in abnormality. 46(86.8%) males and 26(70.3%) females had disc desiccation but multi-level disc osteophyte complexes demonstrated more in females11(29.7%) . The details are summarized in Table I.

Overall 82 patients (91.1%) had diffuse disc bulge at L5-S1 spinal level. It is more pronounced in males at L4-5 and L5-S1 level 49(92.5%) than in females 34(91.9%) at L4-5 and 33(89.2%)at L5-S1 level with mild to moderate spinal canal stenosis. The narrowing of Neural foramen seen almost similar at L4-5 in both gender but more at L5-S1 in females 35(94.6%) as compared to males 49(92.5%) with nerve root compression. Female patients had noticeable hypertrophy of facet joint and ligamentum flavum at L4-L5 and L5-S1 level. On the whole male patients tended to have slightly more disc degenerative changes than females. (Table II-A and II-B).

DISCUSSION:

The current study compared imaging findings of both males and females with low back pain and demonstrated that disc generation is slightly more commonly seen in males than females. The males were found to be more affected with mild and moderate spinal canal stenosis at Level L4-L5 and L5-S1 than females. These result differs from general clinical

Table 1: Demographics data (n=90)

Demographics		Males Mean±SD / n (%)	Females Mean±SD / n (%)	P-value
Age (years)		44.45±14.48	44.91±17.45	
Radiation of Pain	**Right Lower Limb**	10(18.9%)	11(29.7%)	0.556
	Left Lower Limb	9(17.0%)	5(13.5%)	
	Both Lower Limb	19(35.8%)	14(37.8%)	
	Absent	15(28.3%)	7(18.9%)	
Duration of Pain	**Days**	9(17.0%)	0(0.0%)	0.029
	Weeks	0(0.0%)	1(2.7%)	
	Months	9(17.0%)	13(35.1%)	
	Years	5(9.4%)	4(10.8%)	
	Unknown	30(56.6%)	19(51.4%)	
Disc Desiccation / Disc Osteophyte Complexes	**Yes**	46(86.8%)	26(70.3%)	0.054
	Multi-level disc osteophyte complexes	7(13.2%)	11(29.7%)	

Table 2 A: Distribution of MRI findings at different spinal levels

Variable		Spinal Level			
		L_2-L_3 n (%)	L_3-L_4 n (%)	L_4 –L_5 n (%)	L_5-S_1 n (%)
Disc Bulge in Males	**Diffuse disc bulge**	1(1.9%)	10(18.9%)	49(92.5%)	49(92.5%)
	Mild Disc bulge	2(3.8%)	26(49.1%)	4(7.5%)	0(0.0%)
	Absent	50(94.3%)	17(32.1%)	0(0.0%)	4(7.5%)
Disc Bulge in Females	**Diffuse disc bulge**	1(2.7%)	10(27.0%)	34(91.9%)	33(89.2%)
	Mild Disc bulge	0(0.0%)	11(29.7%)	3(8.1%)	2(5.4%)
	Absent	36(97.3%)	16(43.2%)	0(0.0%)	2(5.4%)
P-value		0.477	0.185	0.922	0.219
Spinal Canal Stenosis in Males	**Mild**	2(3.8%)	26(49.1%)	9(17.0%)	1(1.9%)
	Mild to moderate	0(0.0%)	5(9.4%)	44(83.0%)	52(98.1%)
	Moderate to Severe	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
	Significant	1(1.9%)	1(1.9%)	0(0.0%)	0(0.0%)
	Nil	50(94.3%)	21(39.6%)	0(0.0%)	0(0.0%)
Spinal Canal Stenosis in females	**Mild**	1(2.7%)	13(35.1%)	7(18.9%)	2(5.4%)
	Mild to moderate	0(0.0%)	6(16.2%)	29(78.4%)	33(89.2%)
	Moderate to Severe	0(0.0%)	0(0.0%)	1(2.7%)	1(2.7%)
	Significant	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
	Nil	36(97.3%)	18(48.6%)	0(0.0%)	1(2.7%)
P-value		0.673	0.407	0.464	0.277

perception that females are more likely to have intervertebral disc degeneration. Wang YX et al studied high prevalence of disc space narrowing in elderly women than men. [11] Studies demonstrated that patients with acute pain of severe intensity in lower back region usually have high probability of disc herniation.[12] In the study by A.K. Kohat et al, facet joint arthropathy seen in 75% of patients and compression of nerve root in 72.2%, more commonly seen in females at L4-L5 level in chronic low back pain. [9] One more research demonstrated that main MRI imaging features of disc herniation are usually at L4-L5 and L5- S1 levels in both genders.[13] These imaging features are in line with one more study which also showed the evidence that the spinal canal was smallest in both men and women at the level of L5-S1 and widest at L1-L2.[14]

Our study shows the average age 45 years (mean age 44.64 years) in patients with complaints of low back ache. A.K. Kohat et al explained an average age 41 years in patients with chronic low back pain.[9] Schröder C et al. and Jensen RK et al. provided evidence of the degenerative changes on

Table 2 B: Distribution of MRI findings at different spinal levels

Variable		Spinal Level				P-value
		Males		Females		
		Yes n (%)	No n (%)	Yes n (%)	No n (%)	
Neural Foramina Compromise (NFC)	L_2-L_3	3(5.7%)	50(94.3%)	1(2.7%)	36(97.3%)	0.503
	L_3-L_4	37(69.8%)	16(30.2%)	20(54.1%)	17(45.9%)	0.127
	L_4 –L_5	53(100.0%)	0(0.0%)	37(100.0%)	0(0.0%)	---
	L_5-S_1	49(92.5%)	4(7.5%)	35(94.6%)	2(5.4%)	0.689
Nerve Root Compression (NRC)	L_2-L_3	3(5.7%)	50(94.3%)	1(2.7%)	36(97.3%)	0.503
	L_3-L_4	24(45.3%)	29(54.7%)	10(27.0%)	27(73.0%)	0.079
	L_4 –L_5	52(98.1%)	1(1.9%)	37(100.0%)	0(0.0%)	0.401
	L_5-S_1	49(92.5%)	4(7.5%)	35(94.6%)	2(5.4%)	0.689
Ligamentum Flavum Hypertrophy	L_2-L_3	0(0.0%)	53(100.0%)	0(0.0%)	37(100.0%)	---
	L_3-L_4	3(5.7%)	50(94.3%)	0(0.0%)	37(100.0%)	0.141
	L_4 –L_5	12(22.6%)	41(77.4%)	9(24.3%)	28(75.7%)	0.853
	L_5-S_1	12(22.6%)	41(77.4%)	8(21.6%)	29(78.4%)	0.963
Facet Joint Hypertrophy	L_2-L_3	1(1.9%)	52(98.1%)	0(0.0%)	37(100.0%)	0.401
	L_3-L_4	3(5.7%)	50(94.3%)	4(10.8%)	33(89.2%)	0.329
	L_4 –L_5	27(50.9%)	26(49.1%)	25(67.6**%)**	12(32.4%)	0.116
	L_5-S_1	32(60.4%)	21(39.6%)	27(73.0%)	10(27.0%)	0.216

MRI were more common over 50 years of age in females. [15, 16]

We evaluated that disc desiccation is more in male whereas A.K. Kohat et al. mentioned disc desiccation as the most frequently seen disc issue which is slightly more in females. [9] Liyew WA et al. supported the disc disease as a most commonly seen feature in low back pain. [17] It was observed in our study that disc bulges at L4-L5 and L5-S1 seen in patients with low back ache. This type of relation had also been discussed and published as lumbar degenerative spinal condition affecting nearly 50% of patients presenting with lower back pain with female preponderance.[18]

The pathologies of lumbosacral region can detoriate the clinical manifestations of pain radiating to legs so to rule out, the magnetic resonance neurography (MRN) of plexus of lumbosacral region is helpful for diagnosing the nerve problems. [19,20]

The current study has its limitations as it was done at a single center having small sample size and few variables like pain severity and management options were not highlighted, similar study was done by Vagaska, E et al , that was carried out to see the relationship of MRI features with the extent of dysfunction or the severity of low backache.[21] The current study and its findings may not account for the overall disease load in the whole population. However, the study highlighted that lower lumbar disc disease is more in males as compared to females with P value 0.054. It also showed the important role of MRI Lumbar spine in patients with chronic lower back pain and their clinical relevance of radiculopathy.

CONCLUSION:

Lower Lumbar disc disease is a common problem of patients visiting health care facilities showing disc space narrowing and bulges slightly more in our male population than females. MRI provides better assessment of lower back pain in both genders, providing early diagnosis, management and increasingly better outcome.

Authors Contribution:
Nazia Azeem: Literature search, conception study design, data collection and compilation
Muhammad Anwar: Data analysis and interpretation, manuscript writing
Shazia Kadri: Data collection and compilation, Research collaboration

REFERENCES:

1. Hoy D, March L, Brooks P, Blyth F, Woolf A, Bain C, Williams G, Smith E, Vos T, Barendregt J, Murray C. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. Annals of the rheumatic diseases. 2014 Jun 1;73(6):968-74. doi: 10.1136/annrheumdis-2013-204428.
2. Wu A, March L, Zheng X, Huang J, Wang X, Zhao J, Blyth FM, Smith E, Buchbinder R, Hoy D. Global low back pain prevalence and years lived with disability from 1990 to 2017: estimates from the Global Burden of Disease Study 2017. Ann Transl Med. 2020;8(6):299. doi:10.21037/atm.2020.02.175.

3. Alghwiri A, Marchetti G. Occupational back pain among schoolteachers in Jordan: estimated prevalence and factors associated with self-reported pain and work limitations. Int J Occup Saf Ergon. 2018;24(3):341–346. doi:10.1080/ 10803 548.2016.1247605
4. Suliman M. Prevalence of low back pain and associated factors among nurses in Jordan. Nurs Forum. 2018;53(4): 425–431. doi:10.1111/nuf.12269
5. Rathore FA, Attique R, Asmaa Y. Prevalence and perceptions of musculoskeletal disorders among hospital nurses in Pakistan: a cross-sectional survey. Cureus. 2017;9(1). DOI: 10.7759/ cureus.1001
6. Yin, J., Liu, Z., Li, C. et al. Effect of facet-joint degeneration on the in vivo motion of the lower lumbar spine. J Orthop Surg Res 15, 340 ,2020. Doi .10.1186/s13018-020-01826-z
7. Wong AYL, Karppinen J, Samartzis D. Low back pain in older adults: risk factors, management options and future directions. Scoliosis Spinal Disord. 2017;12:14. doi: 10.1186/ s13013-017-0121-3.
8. Qaseem A, Wilt TJ, McLean RM, et al.: Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017, 166:514-30. DOI :10.7326/M16-2367
9. Kohat AK, Kalita J, Ramanivas S. Clinical significance of magnetic resonance imaging findings in chronic low backache. The Indian journal of medical research. 2017; 145(6):796. doi: 10.4103/ijmr.IJMR_1653_14
10. Yousif S, Musa A, Ahmed A, Abdelhai A. Correlation between Findings in Physical Examination, Magnetic Resonance Imaging, and Nerve Conduction Studies in Lumbosacral Radiculopathy Caused by Lumbar Intervertebral Disc Herniation. Advances in Orthopedics. 2020;24(34);24 -27. doi: 10.1155/2020/9719813
11. Wang YX, Griffith JF, Zeng XJ, Deng M, Kwok AW, Leung JC, Ahuja AT, Kwok T, Leung PC. Prevalence and sex difference of lumbar disc space narrowing in elderly chinese men and women: osteoporotic fractures in men (Hong Kong) and osteoporotic fractures in women (Hong Kong) studies. Arthritis Rheum. 2013;65(4):1004-10. doi: 10.1002/art.37857. PMID: 23335175; PMCID: PMC3618501.
12. Fjeld OR, Grøvle L, Helgeland J, Småstuen MC, Solberg TK, Zwart JA, Grotle M. Complications, reoperations, readmissions, and length of hospital stay in 34 639 surgical cases of lumbar disc herniation. Bone Joint J. 2019;101-B(4):470-477. doi: 10.1302/0301-620X.101B4.
13. Singh R, Kumar P, Wadhwani J, Yadav RK, Khanna M, Kaur S. A comparative study to evaluate disc degeneration on magnetic resonance imaging in patients with chronic low back pain and asymptomatic individuals. Journal of Orthopaedics, Trauma and Rehabilitation. January 2021. doi:10.1177/22104917211039522
14. Griffith JF, Huang J, Law S.W ,et al. Population reference range for developmental lumbar spinal canal size. Quant Imaging Med Surg 2016:6(6);671-679. doi: 10.21037/ qims. 2016.12.17
15. Schröder C, Nienhaus A. Intervertebral Disc Disease of the Lumbar Spine in Health Personnel with Occupational Exposure to Patient Handling-A Systematic Literature Review and Meta-Analysis. Int J Environ Res Public Health. 2020;17(13) :4832. doi: 10.3390/ijerph17134832.
16. Jensen RK, Jensen TS, Koes B, Hartvigsen J. Prevalence of lumbar spinal stenosis in general and clinical populations: a systematic review and meta-analysis. Eur Spine J. 2020;29(9): 2143-2163. doi: 10.1007/s00586-020-06339-1
17. Liyew WA. Clinical Presentations of Lumbar Disc Degeneration and Lumbosacral Nerve Lesions. Int J Rheumatol. 2020;2020:2919625. doi: 10.1155/2020/2919625.
18. Deer T, Sayed D, Michels J, Josephson Y, Li S, Calodney AK. A review of lumbar spinal stenosis with intermittent neurogenic claudication: disease and diagnosis. Pain Med 2019; 20: S32–44. doi: 10.1093/pm/pnz161.
19. Beynon R, Elwenspoek MMC, Sheppard A, et al The utility of diagnostic selective nerve root blocks in the management of patients with lumbar radiculopathy: a systematic review. BMJ Open 2019;9:e025790. doi: 10.1136/bmjopen-2018-025790
20. Ibrahim, I, Skoch A, Herynek V, et al. Magnetic resonance tractography of the lumbosacral plexus: Step-by-step. Medicine: February 12, 2021;100(6): p e24646 doi: 10.1097/ MD. 0000000000024646
21. Eve V, Alexandra L, Iva S, Eva V, et al. Do lumbar magnetic resonance imaging changes predict neuropathic pain in patients with chronic non-specific low back pain?, Medicine: 2019: 98(17);pe15377 doi: 10.1097/MD.0000000000015377

Original Article **Open Access**

Outcome of Indoor Covid Cases with Moderate to Severe Disease; Convalescent Plasma Transfusion vs Conventional Therapy

Lubna Meraj, Muhammad Usman, Nadia Shams, Muhammad Umar, Sidra Tahir, Nasim Akhtar, Muhammad Khalid Mehmood Randhawa, Asif Majid, Ashar Alamgir

ABSTRACT

Objectives: Global COVID-19 epidemic has been therapeutic challenge. Convalescent plasma is observed to improve clinical outcomes. This research aims to study whether convalescent plasma therapy reduces the mortality and duration of hospitalization in moderate to severe Covid.

Study Design and Setting: This interventional study was conducted after ethical approval at RIUT COVID-19 center from1st June-30th Nov 2020.

Methodology: Hundred Covid patients included; Total 100 hospitalized adult SARS Cov-2 PCR positive with moderate to severe disease who agreed for convalescent plasma transfusion were included. Fifty in plasma transfusion group and fifty in conventional therapy group. T*hose with* contraindications for plasma transfusion, delayed presentation, indoor stay <5 days were excluded. Convalescent plasma was obtained from donors with prior documented SARS CoV-2 infection meeting donor eligibility criteria. 50 cases received convalescent plasma and50 received conventional therapy. Hospital stay and outcome documented.

Results: Amongst 100 Covid cases; 44 females and 56 males; mean age 57.88+11.95 years, 74% had moderate covid and 26% severe. Fifty cases received conventional therapy for Covid and 50 received plasma transfusion. Both groups comparable for gender, age, smoking, obesity, and disease severity. Invasive ventilation administered in 25% and was associated with mortality (p=0.004). Mortality observed in 29 cases; 20(69%) in plasma transfusion group Vs. 09(31%) in conventional therapy group (p=0.015). The hospital stay was comparable between two groups The relative risk ratio was 2.22 with 95% CI (1.12-4.39).

Conclusions: There was no therapeutic benefit in Covid patients treated with convalescent plasma as compared to conventional treatment.

Keywords: SARS COV-2, Convalescent plasma transfusion, COVID PCR, Donor Eligibility Criteria.

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INTRODUCTION:

The Corona virus (SARS-Cov-2) was first detected in 2019 in Wuhan province of China.[1] The novel corona virus leads to various degrees of severity of symptoms from mild fever, myalgia to severe respiratory distress. Several medications and therapeutic modalities are under trials for safety and efficacy. To date 153 million cases reported worldwide with 3.2 million deaths. These figures are on persistent rise despite of ongoing vaccination process worldwide. The World Health Organization estimates that serious illness may occur in as many as 13.8% of cases and 6.1% are critical.[2] When

fulminant, patients may develop sepsis, acute respiratory distress syndrome (ARDS), and/or multiple organ failure which are not unique to coronavirus.[3]

The convalescent plasma is retrieved from the recovered cases of a particular disease and has been used since more than a century for management of several infectious diseases including the 2003 SARS-CoV-1 epidemic, the 2009-2010 H1N1 influenza virus pandemic, and the 2012 MERS-CoV epidemic.[4] The convalescent plasma that contains antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been studied for management of patients with COVID-19. Studies have demonstrated significant safety profile and efficacy of convalescent plasma. The benefit was particularly observed in patients less than 80 years age and by administration of plasma with high titers of antibodies.[5] However, long term data denies the difference in reduction of mortality based on titers of antibodies in plasma[6] or the administration of plasma versus placebo.[7]

The SARS-Cov-2 has been a therapeutic challenge for the health care system. The infectiousness and lethality of the virus demands extensive and fruitful efforts to control the spread of epidemic as well as definitive cure for illness. The therapeutic aims are not only to target the virus, but also the management of complex phenomena of cytokine storm, inflammation, endothelial dysfunction, coagulopathy and multi-organ failure. These are short-term observations of the COVID, however since the time to emergence of COVID is rising, certain long-term complications including interstitial lung disease, cardiovascular and cerebrovascular events are claiming more lives.

There has been limited and contradictory regional data addressing convalescent plasma in COVID patients.[8] Current study may provide a reference data and enable us to determine and compare the safety, efficacy and prospects of convalescent plasma in our patients.

METHODOLOGY:

This interventional study was conducted at Rawalpindi Institute of Urology that is serving as COVID-19 infection isolation and management center. Study was conducted from 1st June 2020 to 30th November 2020. Ethical approval was obtained from ethical review board of RMU (ref# 55/IREF/RMU/2020). Covid was a novel disease, with the approved therapy of convalescent plasma that was also new and not time tested regarding the Covid therapy. There were certain limitations to sample size calculation with varying prevalence of cases during pandemic. Hence, during the selected time frame for the study, all the patients meeting the inclusion and exclusion criteria were selected by consecutive sampling.

Hundred indoor adult SARS COV-2 (PCR positive) cases of both genders were included by consecutive sampling. Moderate to severe Covid cases meeting plasma transfusion therapy criteria were selected. Mild disease, contraindications for plasma transfusion, who changed decision regarding plasma transfusion or left against medical advice were **excluded**. Fifty cases were included each in plasma transfusion and conventional therapy group. Patients were clinically classified as mild, moderate, severe, and critical according to National Institute of Health, Pakistan guidelines.[9]

The selected patients were randomly allocated into two equal groups according to computer generated random numbers table. Fifty cases were included in plasma transfusion group and conventional therapy group each. Written consent was obtained from the patients or their first degree relative.

Operational Definitions

Moderate COVID disease is defined as

- evidence of lower respiratory disease during clinical assessment or imaging
- SpO_2 =94% on room air at sea level.

Severe COVID disease is defined as one or more of the following:

- Shortness of breath (dyspnea).
- Respiratory frequency = 30/min.
- Blood oxygen saturation = 93%.
- Partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300.
- Lung infiltrates > 50% within 24 to 48 hours.

Life-threatening COVID disease is defined as one or more of the following:

- respiratory failure.
- septic shock.
- multiple organ dysfunction or failure.

Demographic details and history were obtained including symptoms and co-morbid conditions. Clinical evaluation and laboratory investigations were conducted (i.e., blood complete picture, d-dimers, C reactive protein, LDH, creatinine, ALT, ECG, Chest x-ray, CT-scan chest, arterial blood gases).

Donor Eligibility Criteria: COVID-19 convalescent plasma is collected from individuals who meet the following qualifications:

- Evidence of COVID-19 documented by a laboratory test either by a diagnostic test (e.g., nasopharyngeal swab) at the time of illness OR positive serological test for SARS-CoV-2 antibodies after recovery
- Complete resolution of symptoms at least 14 days before the donation. A negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor.

The convalescent plasma was obtained from donors with prior documented SARS CoV-2 infection meeting the donor

eligibility criteria. There were several difficulties regarding plasma acquirement like arranging and screening donors for anemia, calcium, Hepatitis-Bs Ag, anti HCV, HIV. Several donors were not included due to inability to fulfill the screening criteria. The donor plasma which did not contain the antibodies or had less antibody titer were excluded. Plasma extraction itself was a cumbersome process. Plasma was replaced with normal saline; hence the donor didn't get dizziness and dehydration due to loss of volume. Then plasma was either transferred or stored in blood bank in BBH or handed over to attendant for recipient treatment in RIUT.

Apart from the donor issues, few eligible recipients had contraindications for plasma transfusion i.e., multi-organ failure, cytokine release syndrome and renal failure. Patients were provided recommendation and eligibility for plasma transfusion therapy in addition to conventional therapy. Those who agreed for plasma transfusion were included. The selected cases received plasma from donor in addition to conventional therapy with all the pre-requisites for plasma transfusion. Patients were managed and monitored till the recovery and discharge or death.

Record keeping: A health care provider who is participating maintained the records for the COVID-19 convalescent plasma unit(s) administered to the COVID-19 patients. Record included the unique identification number (e.g., the ISBT donation identification number).

All the details were entered on specially designed proforma and data was analyzed by SPSS version 22. Quantitative variables (age, duration of hospital stay) presented as mean and standard deviation. Qualitative variables (gender, Covid severity, modes of ventilation, outcome, co-morbids) presented as frequencies and percentages. Chi-square test applied to study association of qualitative variables with modes of therapy and outcome, fisher's exact test for qualitative variables having less than five values and student-t test for quantitative variables. P-value<0.05 considered as statistically significant. Data presented as tables, bar graphs and pie charts.

RESULTS:

Amongst 100 cases of moderate to severe covid, there were 44 females and 56 males. The mean age was 57.88 +11.95 years with the range of 28-83 years. Obesity (BMI>30 kg/m^2) was found in 33(33%). Smoking was reported by 9(9%) patients. Regarding the severity of Covid, 74(74%) cases had moderate disease and 26(26%) had severe disease.

Fifty cases received the conventional therapy for covid and 50 cases received plasma in additional to conventional therapy. Both the groups had equal number of male and female cases ($p > 0.05$). The mean age in conventional therapy group was 55 +12.9 years Vs. 60.7+10.26 years in plasma group (table 1; p=0.081). Both groups were comparable in terms of obesity (p=0.351) and smoking (p=0.193).

The mean level of antibodies was 17.12 (range 1.82-78.79). During plasma transfusion, 45(45%) cases had no immediate adverse reaction during or after plasma transfusion. Fever with shivering was seen in 2(4%), skin rash in 1(2%) and tachycardia in 2(4%) cases.

Patients received multiple modes of oxygenation and ventilation. 17(17%) were managed by oxygen via nasal canula alone. High flow oxygen was given in 11(11%) cases. 42(42%) cases were managed by non-invasive ventilation and 25(25%) by invasive ventilation. Only 05(5%) were the cases that didn't required any oxygen therapy. Regarding 25 cases that received invasive ventilation, 18(72%) belonged to plasma transfusion group and 07(28%) conventional therapy group with a significant difference (p=0.004).

Among 74 cases with moderate covid, 39(52.7%) were from plasma transfusion group and 35(47.3%) were from conventional therapy group. There were 26(26%) cases having severe covid, 11(42.3%) were from plasma transfusion group and 15(57.7%) were from conventional therapy group. There was no statistical difference in severity of disease between two groups (p=0.362).

The main outcome of the study showed that 71(71%) cases were successfully treated and discharged from hospital. Among these 71 recovered cases, 30(42.3%) were from plasma transfusion group and 41(57.7%) were from conventional therapy group. Mortality was observed in 29 out of 100 cases (i.e., 29%). 20(69%) of the deaths were from plasma transfusion group and 09(31%) deaths were from conventional therapy group (p=0.015).

In terms of duration of hospital stay, there was no difference in mean hospital stay between two groups (p=0.133). The mean hospital stay was 13 days in conventional therapy group and 15 days in plasma transfusion group. There was no association of mortality with gender, age, duration of hospital stays. However, mortality was found to have significant association with severity of Covid, obesity and invasive ventilation ($p<0.05$; Fig 1, 2 & Table 2).

The Relative risk ratio was calculated through Medcalc.[10] The relative risk (RR) or risk ratio is the ratio of the probability of an outcome in an exposed group to the probability of an outcome in an unexposed group. Together with risk difference and odds ratio, relative risk measures the association between the exposure and the outcome.[11] In this study the exposed group was that of plasma therapy and conventional group was the unexposed group. The outcome was measured in terms of mortality and survival. The relative risk ratio was calculated by Medcalc software. The results were achieved are presented in table 3.

DISCUSSION:

This study highlights an important treatment option which has been used in many Covid patients in current pandemic

Table 1: The demographic variables, disease severity, modes of ventilation and outcome of plasma therapy Vs. Conventional therapy in Covid cases (n=100)

Variables	Amongst all n=100	Plasma therapy group n=50	Conventional therapy group n=50	*p-value*
Age (mean + SD years)	57.88 +11.95 28-83 years	60.7+10.26	55 +12.9	0.081
Duration of Hospital stay (mean + SD days)	14.17 + 7.79 5-45 days	15.46 + 8.71	12.88 + 6.59	0.133
Gender - Females - Males	 44(44%) 56(56%)	 22(50%) 28(50%)	 22(50%) 28(50%)	1.000
Obesity - Obese - Non-obese	 34(34%) 66(66%)	 18(52.9%) 32(48.5%)	 16(47.1%) 34(51.5%)	0.673
Smoking - Smokers - Non-smokers	 9(9%) 91(91%)	 04(44.4%) 46(52.3%)	 05(55.6%) 42(47.7%)	0.193
COVID Severity - Moderate - Severe	 74(74%) 26(26%)	 39(52.7%) 11(42.3%)	 35(47.3%) 15(57.7%)	0.362
Outcome - Discharged - Expired	 71(71%) 29(29%)	 30(42.3%) 20(69%)	 41(57.7%) 09(31%)	0.015
Modes of Ventilation - None - Nasal canula - High flow nasal canula - NIV - Invasive ventilation	 05(5%) 17(17%) 11(11%) 42(42%) 25(25%)	 0(0%) 04(23.5%) 07(63.6%) 21(50%) 18(72%)	 05(5%) 13(76%) 04(36.4%) 21(50%) 07(28%)	0.004
Co-morbids - Diabetes Mellitus - HTN - IHD - Asthma - COPD - CKD - Hypothyroid	 55(55%) 62(62%) 17(17%) 11(11%) 05(5%) 05(5%) 07(7%)	 29(52.7%) 32(51.6%) 09(52.9%) 05(45.5%) 01(20%) 02(40%) 02(28.5%)	 26(47.2%) 30(48.4%) 08(47.1%) 06(54.5%) 04(80%) 03(60%) 05(71.4%)	0.546 0.680 0.790 0.749 0.362 1.000 0.436

(Test of significance; Chi-square, Fisher's exact test, student t-test; significant p < 0.05)

Figure 1: Bar graph representing expiry in Moderate Vs. Severe Covid cases (n=100)

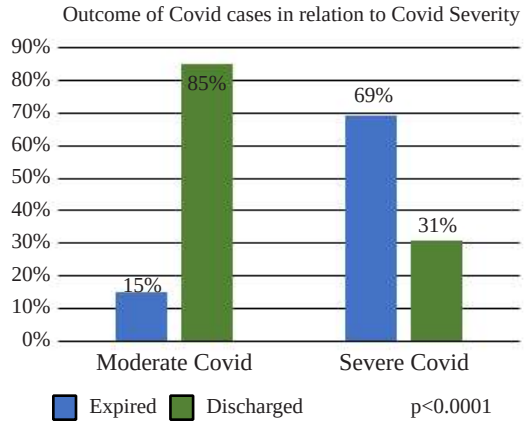

Figure 2: Bar graph representing expiry in Obese Vs. Non-obese Covid cases (n=100)

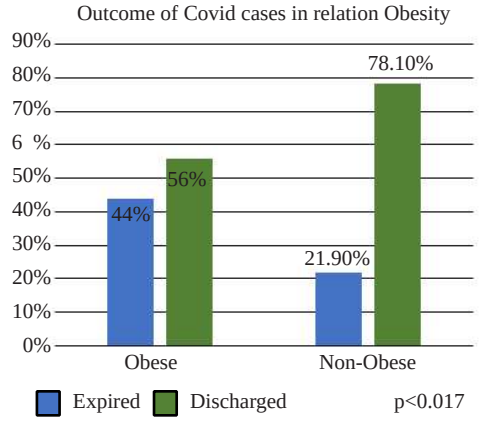

Table 2: Outcomes of covid cases managed by various modes of ventilation (n=100)

Modes of Ventilation	Among all (n=100)	Expired (n=29)	Discharged (n=71)	P-value
Invasive Ventilation	25(25%)	19(76%)	06(24%)	*<0.0001*
Non-invasive ventilation	42(42%)	05(11.9%)	34(81%)	
High flow oxygen	11(11%)	05(45.5%)	06(54.5%)	
Nasal canula	17(17%)	0(0%)	17(100%)	
None	05(5%)	0(0%)	05(100%)	

(Test of significance, Fisher's exact test; significant p<0.05)

Table 3: The table representing relative risk ratio calculated by Medcalc software.

Relative risk	2.2222
95% CI	1.1235 to 4.3956
Z static	2.294
Significance level	P=0.0218
NNT (Harm)	4.545

scenario in Pakistan. The study was done in a public setup hospital which is reflective of the resource limited hospital's management plans amid the Covid Crisis. There were two groups of Covid patients who were well matched in terms of the confounding factors like age, gender, obesity, smoking status and Covid severity. The *P-value* calculated showed more than 0.05 value in each factor, which showed no statistical significance. The mean age was fifty-seven years. Thus, it can be inferred that the age group above 50 years have higher tendency for need of admission. The strong age gradient has been observed by Varity et al as a risk factor for covid associated mortality.[12] Both of the groups were comparable in terms of age and gender. Among all cases there were 56% males as compared to 44% females.

There was high burden of co-morbid conditions, particularly diabetes and hypertension in our admitted cases. This reflects the overall regional prevalence of diabetes and hypertension. Studies have demonstrated that patients with these co-morbids are prone to be admitted and develop the severe forms of disease. However, both groups were comparable in terms of co-morbids, minimizing the likelihood of this as a contributory factor for mortality.

There was no significant difference in mean hospital stay between plasma therapy and conventional therapy groups. A study by RECOVERY collaborative group found no benefit of convalescent plasma regarding the proportion of patients discharged within 28 days.[13]

Certain confounding factors, other than age and gender were disease severity and need for ventilation. Both the groups had no statistical difference in disease severity. However, the plasma transfusion group had more cases that required invasive ventilation (i.e., 73%) as compared to lesser number of conventional therapy group cases (27%) requiring ventilation. Hence, the need for invasive ventilation may be interpreted as one of the contributing factors for poor outcome in plasma therapy group.

The indications for invasive ventilation include hypoxia, severity of lung involvement, multi-organ failure, the rapid progression of disease, deteriorating GCS due to hypoxia and other metabolic causes.[14] Authors recommend that these should be studied in future research. The higher number of patients in plasma group required invasive ventilation as compared to the conventional group as calculated P was less than 0.05. It can be inferred as the group which received plasma was sicker, thus requiring the ventilator support as compared to the other group. A total of 100 patients were included in the study out of which a group of 50 patients were given conventional treatment and the other group of 50 patients was given Convalescent plasma in addition to Conventional treatment. The donor plasma antibody titer was confirmed before administration of the plasma. The results showed statistical significance in the primary outcome of both groups.

Contrary to the clinical assumption the mortality was higher in the plasma group as compared to the conventional group. The Relative Risk ratio was more than 1 which means that the plasma group was having more mortality as compared to the other group. 95% confidence interval (1.12-4.39) calculated showed a wide range thus there is limited precision of the result value. It could be because of small number of patients and may be the study was underpowered. Or the patients with plasma group were sicker than the conventional group.

The plasma acquired from the screened donors had a wide range of antibodies titer ranging from 1.82 to 78.79. The variability of antibody titer could have changed the effectiveness of therapy among the plasma group.[15] Certain contraindications to donor and recipient eligibility also played a role in difficulty in selecting the appropriate candidates for plasma therapy.[16] There were no acute events or major adverse reactions during plasma transfusion, we may conclude that though it's a safe procedure, yet its efficacy is questionable that needs to be further evaluated.

We observed a death rate of 29%. Sheng et al observed a higher death rate of 38% in moderate to severe Covid cases in a study conducted in Wuhan China that is considered as epicenter of epidemic.[17] The reasons of such higher mortality could be that moderate to severe Covid cases were included, while mild and outdoor cases were excluded. Patients who require indoor care are already sick and high-risk cases. Also, during the earlier phase of epidemic, there was no vaccine available or approved that could have led to severe disease, need for ventilation and involvement of lung parenchyma.[18] The mortality of Severe Covid disease requiring mechanical ventilation has been found to vary in different studies. Namendy et al has reported a very high mortality of 73% in a Mexican study.[19] However, Mitra et

al has reported a comparatively lower mortality (15%) in a Canadian study.[20] There has been a debate regarding the modes of ventilation and settings of the ventilator as well; particularly in Covid cases.[21] Most of guidelines suggest the ventilator settings as recommended for ARDS cases earlier. We had approx. 1/4th of our patients on invasive ventilation (25%) and there was significant association of invasive ventilation with mortality ($p<0.0001$). Higher number of patients in plasma group received invasive ventilation, this is additional contributory factor to higher mortality in plasma group.

This study provides us data about the treatment modality used in a novel disease that is yet to be explored and needs urgent and worldwide research in view of its high mortality and global burden. Limited regional data is available, though several international studies have been conducted that show variety of outcomes. This may act as a benchmark for future studies as well as comparison to international data. There were certain limitations of the study like being a single centered study. The day of illness on which each patient of plasma group received the convalescent plasma was not observed in the study which could also affect the results. The antibodies titer post administration of plasma could not be measured due to budget constraints. It was an open labelled trial with no randomization due to ethical issues regarding consent of the plasma administration. The study was underpowered because of resource limitation in a public sector hospital therefore type 2 error cannot be excluded. The results of moderate severity plasma group cannot be extrapolated as the moderate severity patient would have recovered without the plasma due to lesser severity of the disease. Hence authors suggest careful interpretation of data and suggest further research in this context.

CONCLUSION:

There was no therapeutic benefit found in Covid patients treated with convalescent plasma as compared to conventional treatment. Although further research is required to have a clear understanding, but the use of convalescent plasma shouldn't be considered as a treatment of choice.

Authors Contribution:
Lubna Meraj: Data Collection, Conception, design analysis
Muhammad Usman: Data collection, design, analysis
Nadia Shams: Data collection. Analysis/interpretation of data
Muhammad Umar: Data collection, literature review, write up, referencing
Sidra Tahir: Data collection, conception, design
Nasim Akhtar: Data collection, conception, design
Muhammad Khalid Mehmood Randhawa: Data collection, write up, plasma preparation, donor selection
Asif Majid: Data collection, write up, recipient selection
Ashar Alamgir: Data collection, write-up plasma preparation donor selection

REFERENCES:

1. National Health Commission of the People's Republic of China. Update on the novel coronavirus pneumonia outbreak (Feb 16, 2020). https://www.nhc.gov.cn/ xcs/yqtb/202002/ 18546da875d74445bb537ab014e7a1c6.shtml.
2. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). 16–24 February 2020. https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
3. Chang JC. Sepsis and septic shock: endothelial molecular pathogenesis associated with vascular microthrombotic disease. Thromb J. 2019;17:10. doi: https://doi.org/10.1186/s12959-019-0198-4.
4. Keith P, Day M, Perkins L, Moyer L, Hewitt K, Wells A. A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19. Crit Care. 2020;24(1):128. Published 2020 Apr 2. doi: https://doi.org/10.1186/s13054-020-2836-4.
5. Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. Mayo Clin Proc 2020;95:1888-97. doi: https://doi.org/10.1016/j.mayocp.2020.06.028.
6. Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. medRxiv. 2020 Aug 12:2020.08.12. 20169359. doi: https://doi.org/10.1101/ 2020.08.12.20169359.
7. Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, et al. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. N Engl J Med. 2021 Feb 18;384(7):619-629. doi: https://doi.org/10.1056 /NEJMoa 2031304.
8. Avendano-Sola C, Ramos-Martinez A, Munez-Rubio E, Ruiz-Antoran B, de Molina RM, et al. Convalescent plasma for COVID-19: a multicenter, randomized clinical trial. MedRxiv. 2020 Jan 1. doi: https://doi.org/10.1101/2020.08.26.20182444.
9. National Institute of Health: COVID-19 . (2020). Accessed: April 24, 2022: DOI: https://www.nih.org.pk/novelcoranavirus-2019-ncov/
10. Medcalc—Relative Risk Calculator; 2017; Available online: https://www.medcalc.org/calc/relative_risk.php (accessed on 25th Sept 2021).
11. Sistrom CL, Garvan CW (January 2004). "Proportions, odds, and risk". Radiology. 230 (1): 12–9. doi: https://doi.org/ 10.1148/ radiol.2301031028.
12. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. The Lancet infectious diseases. 2020 Jun 1;20(6):669-77. doi: https://doi.org/10.1016/S1473-3099(20)30243-7.
13. Recovery Collaborative Group. "Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial." Lancet (London, England) vol. 397,10289 (2021): 2049-2059. https://doi.org/10.1016/S0140-6736(21)00897-7.
14. Carter C, Osborn M, Agagah G, Aedy H, Notter J. COVID-19 disease: invasive ventilation. Clinics in Integrated Care. 2020;1:100004. doi: https://doi.org/10.1016/j.intcar.2020. 100004.

15. Madariaga ML, Guthmiller JJ, Schrantz S, Jansen MO, Christensen C, Kumar M. Clinical predictors of donor antibody titre and correlation with recipient antibody response in a COVID-19 convalescent plasma clinical trial. Journal of internal medicine. 2021;289(4):559-73. doi: https://doi.org/10.1111/joim.13185.

16. Mahapatra S, Pati S. Constraints and challenges in convalescent plasma collection amidst the Covid 19 pandemic- strategies and recommendations to overcome these. Transfus Clin Biol. 2021;28(2):175-79. doi: https://doi.org/10.1016/ j.tracli.2021 .02.003.

17. Sheng, L., Wang, X., Tang, N. et al. Clinical characteristics of moderate and severe cases with COVID-19 in Wuhan, China: a retrospective study. Clin Exp Med 21, 35–39 (2021). doi: https://doi.org/10.1007/s10238-020-00662-z.

18. Antonelli M, Penfold RS, Merino J, Sudre CH, Molteni E, Berry S, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. The Lancet Infectious Diseases. 2021 Sep 1. doi: https://doi.org/10.1016/S1473-3099(21)00460-6.

19. Ñamendys-Silva SA, Gutiérrez-Villaseñor A, Romero-González JP. Hospital mortality in mechanically ventilated COVID-19 patients in Mexico. Intensive Care Med. 2020. doi: https://doi.org/10.1007/s00134-020-06256-3.

20. Mitra AR, Fergusson NA, Lloyd-Smith E, et al. Baseline characteristics and outcomes of patients with COVID-19 admitted to intensive care units in Vancouver, Canada: a case series. CMAJ. 2020;192: E694–701. doi: https://doi.org/10.1503/ cmaj.200794.

21. Möhlenkamp, S., & Thiele, H. (2020). Ventilation of COVID-19 patients in intensive care units. Beatmung von COVID-19-Patienten auf Intensivstationen. Herz, 45(4), 329–331. doi: https://doi.org/10.1007/s00059-020-04923-1.

Original Article **Open Access**

Urological Injuries in Obstetrical and Gynaecological Surgery at Tertiary Care Hospital

Shazia Naseeb, Piranka Kumari, Shaista Rashid

ABSTRACT

Objectives: To determine the frequency of urological injuries in obstetrical and gynaecological surgery.

Study Design and Setting: The Cross Sectional Study was conducted at Department of Obstetrics & Gynaecology, Jinnah Postgraduate Medical Center, Karachi for duration of 6 months from 31st December 2020 to 30th June 2021.

Methodology: A total of 142 patients selected between the ages of 25 to 55 years of age were included. In this study all patients were included who fulfilled the inclusion criteria undergoing obstetric(cesarean section) & gynecological surgeries (laparatomies & hysterectomies). They were enrolled after taking written and informed consent. Risk factors for urological injuries were assessed in terms of indication (risk for surgery), site of urologic injury, duration of surgery and time interval after surgery. Patients having urological injury from other than obstetric and gynecologic surgeries and those who did not give consent were excluded.

Results: Age range in this study was from 25 to 55 years with mean age of 40.20 ± 6.92 years. Majority of the patients 77 (54.23%) were between 41 to 55 years of age. Mean duration of surgery was 62.16 ± 14.52 minutes. Mean time interval after surgery was 37.51± 13.89 hours. In this study, frequency of ureteral injury, urinary bladder injury and mixed injury in obstetrical and gynaecological surgery was found in 01 (0.70%), 19 (13.38%) and 01 (0.70%) patients respectively.

Conclusion: This study concluded that knowledge of pelvic anatomy, careful dissection and patience in difficult cases are the key factors to anticipate and prevent injury.

Keywords: urological injuries in gynaecological surgeries, ureteric injuries, bladder injuries, urological Injuries.

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INTRODUCTION:

Urological injuries in pelvic surgeries are not uncommon and urogeintal system grows with each other, sharing common site of development. Urinary bladder and ureter are in close proximity with uterus[1], which makes them vulnerable to injury in pelvic surgeries[2]. In large number of pelvic surgeries performed for gynaecologial and obstetrical reasons, bladder and ureter are likely to be injured.[3] An estimated 0.3% to 1% of urological injuries occur in gynaecological operations and pelvic surgeries.[4] Studies reported the prevalence of 16.8% for bladder, 9.6% for ureteric injuries in gynecological surgery,[5] and frequency of urological injuries for elective and emergency procedures revealed 0.69%.[6]

Morbidities arising from urological injuries is always frightening for both obstetricians and Gynecologists which leads to longer duration of hospital stay, invasive interventions, repetition of surgery, deterioration of kidney functions and complete loss of kidney potential.[7,8] Urological injury is serious complication in gynecological operataions,[9] and can occur in uncomplicated gynaecological surgeries too when it is done by unskilled hands.[10]

The frequency of urological injuries is dependent on the type of gynaecologic surgery performed, indication of surgery, presence of risk factors like huge cervical and broad ligament fibroids, malignancies especially carcinoma cervix, patients with repeated laparotomies, previous cesarean sections, endometriosis, and distorted anatomy, previous radiation, morbidly adherent placenta, profuse hemorrhage and more in radical hysterectomies.[11]

Gynaecological operations have been revealed to be accountable for 75% of the ureteric injuries. Bladder injuries are twice or thrice times more commonly reported injury than in ureter.[12]

Incontinence of urine resulting from uro-genital fistula is a

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devastating complication which is not only stressful for surgeons but traumatic for patients. Anuria after surgery is an immediate attention seeking problem, quick diagnosis and early intervention can prevent major complications. Failure of primary repair of urological injuries is not only stressful for surgeons but frightening for patients as leaking urine makes them socially limited.[13] Urological injuries in pelvic surgery are categorized into early and late morbidities like bladder and ureteric laceration which can be recognized during the time of operation, and late problems appear in the form of vesicovaginal fistula, ureterovaginal fistula, and ureter stricture, which presents after some period of surgery.[14]

By Good obseterical care, urological injuries can be prevented in obstetric patients but this is unavoidable in difficult gynaecological surgeries. Our main purpose of the study is to identify the burden of bladder and ureteric injuries in the patients undergoing surgical procedures for obstetrical and gynaeclogical reasons in our department of Obstetrics and Gynaecology so strategies could be made to prevent urological complications.

METHODOLOGY:

This study was conducted in Jinnah Postgraduate Medical Centre, Karachi in dept. of OBGYN from the period of 31st December 2020 to 30th June 2021 after approval from the ethical review committee (ERC)of the institute (JPMC) with letter no. F.2-81/2021-GENL/ 57186 /JPMC. This is a cross sectional study. In this study all patients were included who fulfilled inclusion criteria of undergoing obstetric (cesarean section) & gynaecologic surgeries (laprotomies & hysterectomies). They were enrolled after taking written informed consent. Patients excluded from the study were those who developed urological complication and those who did not give consent.

Patient's data was assembled and scrutinized through statistical package for Social Sciences (SPSS) Version 21. Frequency and percentage were calculated for qualitative variables like type of surgery, site of injury, bladder injury and ureter injury. Mean±SD were calculated for quantitative variable i.e. age, duration of surgery and duration of injury. Stratification was done on age, duration of surgery, time interval after surgery, type of surgery and to observe the effect of these modifiers on outcome using Chi-square test. P value =0.05 was considered as significant.

RESULTS:

Patients were included in this study within the age range of 25-55 years, mean age of patients' was 40.20 ± 6.92 years. Most of the patients that is 77 (54.23%) had average age between 41 to 55 years. Mean duration of surgery was 62.16 ± 14.52 minutes. Mean time interval after surgery was 37.51 ± 13.89 hours. Distribution of patients according to indication

Table 1: Stratification of the urological injuries with respect to age

		25-40yrs (n=65)	41-55yrs (n=77)	P-value
Ureteral injury	Yes	00 (0.0%)	01 (1.29%)	0.357
	No	65 (100%)	76 (98.71%)	
Urinary bladder injury	Yes	13 (20.00%)	06 (7.79%)	0.033
	No	52 (80.0%)	71 (92.21%)	
Mixed injury	Yes	01 (1.54%)	00 (0.0%)	0.275
	No	64 (98.46%)	77 (100.0%)	

Table 2: Stratification of the urological injuries with respect to duration of surgery.

		≤60 min (n=62)	>60 min (n=80)	P-value
Ureteral injury	Yes	00 (0.0%)	01 (1.25%)	0.377
	No	62 (100.0%)	79 (98.75%)	
Urinary bladder injury	Yes	07 (11.29%)	12 (15.0%)	0.519
	No	55 (88.71%)	68 (85.0%)	
Mixed injury	Yes	00 (0.0%)	01 (1.25%)	0.377
	No	62 (100.0%)	79 (98.75%)	

Table 3: Stratification of the urological injuries with respect to time interval after surgery

		≤48hrs (n=110)	>48hrs (n=32)	P-value
Ureteral injury	Yes	00 (0.0%)	01 (3.13%)	0.362
	No	110 (100%)	31 (96.87%)	
Urinary bladder injury	Yes	15 (13.64%)	04 (12.50%)	0.002
	No	95 (86.36%)	28 (87.50%)	
Mixed injury	Yes	01 (0.91%)	00 (0.0%)	0.672
	No	109 (99.09%)	32 (100.0%)	

Table 4: Stratification of the urological injuries with respect to type of surgery

		Malignancy (n=34)	Previous surgery (n=56)	Adhesion s (n=27)	Endometriosis/Fibroid (n=25)	P-value
Ureteral injury	Yes	01 (2.94%)	00 (0.0%)	00(0.0%)	00 (0.0%)	0.362
	No	33 (97.06%)	56(100%)	27 (100%)	25(100%)	
Urinary bladder injury	Yes	00 (0.0%)	15 (26.78%)	02(7.4%)	02(8.0%)	0.002
	No	34 (100%)	41 (73.22%)	25 (92.60%)	23 (92%)	
Mixed injury	Yes	00 (0.0%)	01 (1.8%)	00 (0.0%)	00 (0.0%)	0.672
	No	34(100%)	55(98.2%)	27 (100.0%)	25 (100.0%)	

of surgery is shown in Table 1 and 2. In this study, frequency of ureteral injury, urinary bladder injury and mixed injury in obstetrical and gynaecological surgery was found in 01 (0.70%), 19 (13.38%) and 01 (0.70%) patients respectively.

Stratification of the urological injuries with respect to age and duration of surgery is shown in Table, I &II. Stratification of the urological injuries with respect to time interval after surgery and indication of surgery is shown in Table 3 & 4.

DISCUSSION:

Uro-genital system develops with each other and in close relationship so urological complications can be expected in gynecological surgeries. It is reported from a local study that highest number of urological injuries occur in procedures of total abdominal hysterectomy followed by cesarean.[16] Apart from them only few urological complications can result in longer duration of surgery, increase blood loss, prolong hospital stay and may require repeat surgery.

There are many reasons for urological injuries in gynaecological and obstetric surgeries like large fibroid, malignancy, PID, endometriosis, type of surgeries, altered anatomy history of previous surgery, expertise of surgeons and presence of profuse haemorrhage.[17] In the start of advent of laparoscopic surgeries, urological injuries were quite common but with greater advancements in techniques, frequency of urological injuries has decreased yet even now number of ureteric injuries is quite high.[18]

With increased awareness and refinement in surgery, prevalence of urological injuries has markedly reduced as they are recognized per-operatively to be managed well in time before the surgery is completed. Thus, by keeping record of these iatrogenic injuries, risk factors can be easily identified so as to develop preventive strategies and manage long-term complications effectively.

We have conducted this study to find out the prevalence of bladder and ureter injuries in pelvic surgeries done for gynaecological and obstetrical reasons.

In this study, frequency of ureteral injury, urinary bladder injury and mixed injury in obstetrical and gynaecological surgery was found in 01 (0.70%), 19 (13.38%) and 01 (0.70%) patients. A retrospective study by Desai RS reported that bladder injury was consistent and it includes bladder laceration and vesico-vaginal fistula. 71.1% had bladder injury and 23.7% had ureteral injury.[14] Rashmi D and Sunil K quoted prevalance of bladder injury and ureteric injuries to be 0.48% and 0.08% respectively.[18]

We have 13(9.15%) obstetric cases with bladder injury out of which 11(7.7%) cases with morbidly adherent placenta and 2(1.40%) patients were with previos 3 and 4 cesarean sections without MAP; and it was observed that 1 was mix (0.7%) injury of MAP in severe haemorrhage.

Aanwar et.al reported higher incidence of urological injuries (21.7%) compared to our study. They found bladder injuries in 11.7% and ureteric injuries in 4.7% of cases of MAP19. Frequency of bladder injury during obstetrical procedure like caesarean section is repeated as 1% and ureteric injury 0.09%.[20]

Studies of Vandana et al[21] in 2013, Lee et al[22] in 2012, and Choosom et al23 in 2020 reported prevalence of iatrogenic urologic injuries as 0.42%, 0.19% and 0.042% subsequently which is quite low in comparison to our study at Jinnah Postgraduate Medical Centre. This being a tertiary care hospital receives many referrals of complicated cases like morbidly adherent placenta.24

Bladder was the commonly injured organ in our study and injury was mostly recognized at time of surgery with highest cases of morbidly adherent placentas on previous scars. Fibroid uterus and pelvic adhesion were most recurrent indication of pelvic surgeries.

Obstetrical hysterectomy was the commonest procedure with urological injuriesfollowed by total abdominal hysterectomy. Ureter was damaged in one case of Werthiem hysterectomy while one was noted in case of percreta during cesarean hysterectomy in combination with bladder as mix injury during profuse hemorrhage. Both of them were clamped closely with uterine arteries and were identified postoperatively.

Urological injury can be reduced by recognizing ureteric pathway by knowing common sites of injury in case of profound haemorrhage by avoiding blind clamping and careful dissection during mobilization with minimal use of diathermy. Bladder injury is the most evident injury in our study during surgery, while diagnosis of ureteric injury was made postoperatively as in other studies[26] especially if pelvic surgery is done for malignancy of cervix carcinoma, huge pelvic mass, in case of profuse haemorrhage and in patients with repeated surgeries. Ureter integrity can be checked by injecting frusemoid and watch for urinary leakage which gets dilated in cases of obstruction if they are ligated with sutures. Preoperative stenting of ureter helps in identification of uretric injury. Early recognition of urological injury is necessary to manage them properly at time of surgeries with short term morbidity.[27] Whenever patient develops flank pain, fever, hematuria and reduced urine output postoperatively, a strong suspicion must be raised for uretric injury28. Cystoscopy can be considered while other investigations like intravenous pyelography and contrast enhance tomography is ultimately needed for diagnosis and prevention of long-term complications.[29]

Care must be taken while repairing of ureter as it should be stress free. Careful dissection with preservation of blood supply should be done considering proper application of delicate sutures, and attachment of peritoneum and omentum with the repaired ureter, placement of drain to prevent urine collection and putting stent with ureteric catheterization and proximal diversion.[30]

CONCLUSION:

This study concluded that frequency of urinary bladder injury, ureteral injury and mixed injury in obstetrical and gynaecological surgery was found in 13.38%, 0.70% and 0.70% patients. So, we recommend that a proper protocol should be designed in the high risk patients. Complete grasp on ureteric course, its anatomical relations, anticipation of risk factors of urological injuries and pre-operative stenting in difficult gynecological procedures, keeping radiologist on board and meticulous dissection especially in cases of morbidly adherent placenta are the key elements for prevention of urological injuries.

Authors Contribution:
Shazia Naseeb: Concept Design, Data analysis, Manuscript writing.
Piranka Kumari: Data Interpretation, Data collection
Shaista Rashid: Data analysis

REFRENCES:

1. Pal DK. Urological Complications in Obstetrics and Gynaecology. Remed Open Access.2017;2;1072. doi: 10.4103/0974-7796.158502
2. Vaidya B, Chaudhari M, Parmar D, Chaudhari V, Daginawala T, Shah R. Bladder injuries during obstetrical and gynecological surgeries. Intern Surg J. 2017;4(7):2177-80 DOI: https://dx.doi.org/10.18203/2349-2902.isj20172578
3. Bretschneider CE, Casas-Puig V, Sheyn D et al. Delayed recognition of lower urinary tract injuries following hysterectomy for benign indications: A NSQIP-based study. Am J Gynecol. 2019; 221:132.e1. https://doi.org/ 10.1016/j.ajog.2019.03.015
4. Blackwell RH, Kirshenbaum EJ, Shah AS et al.Complications of Recognized an Unrecognized Iatrogenic Ureteral Injury at Time of Hysterectomy: A PopulationBased Analysis. J Urol. 2018; 199:1540. doi: 10.1016/j.juro.2017.12.067. Epub 2018 Mar 2
5. Parveen F. Urinary Tract Injuries During Cesarean Section In Patients With Morbid Placental Adherence•. Journal of Surgery Pakistan. 2021;26(1):9-1.
6. Afzal M. Urological Injuries in Obstetrics and Gynaecological Surgery. JRMC [Internet]. 30Dec.2015 [cited 23Aug.2022]; 19(3):243-6. Availablefrom: https://www. journalrmc. com/index.php /JRMC/article/view/247
7. C.E. Bretschneider, V. Casas-Puig, D. Sheyn, A. Hijaz, C.A. Ferrando, Delayed recognition of lower urinary tract injuries following hysterectomy for benign indications: aNSQIP-based study, Am. J. Obstet. Gynecol. 221 (2019); 132.e1 –132.e13. doi: 10.1016/j.ajog.2019.03.015. Epub 2019 Mar 26.
8. R.H. Blackwell, E.J. Kirshenbaum, A.S. Shah, P.C. Kuo, G.N. Gupta, T.M.T. Turk. Complications of recognized and unrecognized iatrogenic ureteral injury at time of hysterectomy: a population based analysis, J. Urol. 199 (2018) 1540–1545. doi: 10.1016/j.juro.2017.12.067. Epub 2018 Mar 2.
9. Siow A, Nikam YA. Urological complications of laprosopic hysterectomy: a four Year review at KK women's and children's hospital Singapore Med J. 2007;48(3):217-21.
10. Nayak AL, Breau R, Hickling D, Pascali D, Clancy A, Mallick R, et al Factors for Urologic Injury in Women Undergoing Hysterectomy Benign Indication. Journal of Obstetrics and Gynaecology Canada. 2022;44(3):247-54.doi: 10.1016/j.jogc.2021.09.020. Epub 2021 Oct 12
11. Desai RS, Sunil Kumar K. Urological injuries during obstetric and gynaecological procedures: A retrospective analysis over a period of eleven years. Int J Reprod Contracept Obstet Gynecol. 2016;5:1916-20.DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20161690
12. Jadaan A, Anwar S, Anwar S, Bibi S Incidence of Urinary Tract Injuries and nfections Associated with Gynecological Surgeries J Soc Obstet Gynaecol Pak. 2021; 11(2):121-125
13. Sebukoto HR, Semwaga E, Rugakingila RA. Urological injuries following obstetrical and gynecological surgeries. East Central African J Surg. 2016;21(1):148-55. DOI: 10.4314/ecajs.v21i1.139046
14. Lee JS, Choe JH, Lee HS, Seo JT. Urologic complications following obstetric and gynecologic surgery. Korean J Urol. 2012;53(11):795-9. doi: 10.4111/kju.2012.53.11.795
15. Lardas M, Papachristou C, Chrysafis E, Skolarikos A. Lower urinary tract injury during gynaecological and obstetric surgeries: Two years' experience in our centre. Hellenic Urology. 20;30(1).
16. Mansoor M. Non Urological Iatrogenic Ureteric Injuries: Management and Outcome. Journal of Surgery Pakistan. 2021;26(3):97-102.
17. Satitniramai S, Manonai J. Urologic injuries during gynecologic surgery, a 10-year review. Journal of Obstetrics and Gynaecology Research. 2017;43(3):557-63 https://doi. org/10.1111/jog.13238
18. Hwang JH, Kim BW. Laparoscopic radical hysterectomy has higher risk of perioperative urologic complication than abdominal radical hysterectomy: a meta-analysis of 38 studies. Surgical Endoscopy.2020;34(4):1509-21. doi: 10.1007/s00464-020-07366-1. Epub 2020 Jan 17.
19. Desai RS. Urological injuries during obstetric and gynecological procedures: A retrospective analysis over a period of eleven years: Int J Reprod contracept Obstet Gynecol 2016:5(6): 1916-1920. DOI: https://dx.doi.org/ 10.18203/2320-1770.ijrcog20161690
20. Alanwar A, Al-Sayed HM, Ibrahim AM, Elkotb AM, Abdelshafy A, Abdelhadi R et al. Urinary tract injuries during cesarean section in patients with morbid placental adherence: retrospective cohort study. The Journal of Maternal-Fetal & Neonatal Medicine. 2019;32(9):1461-7. doi: 10.1080/14767058.2017.1408069. Epub 2017 Dec 3
21. Kashif U, Riaz N, Ramasubramanian SP, Iles D. Urogynaecological complications in pregnancy. Obstetrics, Gynaecology & Reproductive Medicine. 2021;31(2):42-7. https:// doi.org/10.1016/j.ogrm.2020.12.004
22. Bisht V, Rawat U, Rani K, Chauhan P. Urological injuries in obstetrics and gynaecology". J Evolution Medical Dental Sci. 2013; Vol. 2. DOI:10.14260/jemds/1527
23. Lee JS, Choe JH, Lee HS, Seo JT. Urologic complications following obstetric and gynecologic surgery. Korean J Urol. 2012;53: 795–799. doi: 10.4111/kju.2012.53.11.795

24. Choosom A, Khanuengkitkong S, Choobun T. Urological injuries during gynecologic surgery at Songklanagarind hospital. Thai Journal of Obstetrics and Gynaecology. 2020.

25. Pascal HP, Georges AJ, Naméoua B, Karim PA, Adama O, Alexandre V et al. Urologic Complications after Gynaecologic and Obstetric Surgery at the Urology- Andrology Teaching Clinic of Teaching Hospital of Cotonou. (October): 2014;121–125 DOI: 10.4236/oju.2014.410021

26. Purandare CN, Urological injuries in gynaecology. J Obstet Gynecol India 2007;57: 203- 4.

27. Mann WJ, Arato M, Patsner B, Stone ML. Ureteral injuries in obstetrics and gynecology training program: Etiology and management. Obstet Gynecol 1988; 72: 82-85.

28. Gill EJ, Elser DM, Bonidie MJ, Roberts KM, Hurt WG. The routine use of cystoscopy with the Burch procedure. Am J Obstet Gynecol 2001; 185: 345. doi: 10.1067/ mob.2001 .116732.

30. Tulikangas PK, Weber AM, Larive AB, Walters MD. Intraoperative cystoscopy in conjunction with anti-incontinence surgery. Obstet Gynecol 2000; 95: 794-96 doi: 10.1016/s0029-7844(99)00655-9

Original Article **Open Access**

Impact of Clinical Expertise on Inferior Alveolar Nerve Block Anaesthesia Resulting in Transient Facial Nerve Palsy; A Cross-sectional Study Amid Pakistani Dental Graduates

Rehan Ahmad, Sabeen Masood, Jehan Alam

ABSTRACT

Objective: The purpose of the study is to observe the impact of clinical expertise on inferior alveolar nerve block (IANB) anaesthesia resulting in transient facial nerve palsy (FNP) in dental operators having different levels of clinical experience.

Methodology: This observational cross-sectional study was conducted in the Department of Dentistry, Jinnah Postgraduate Medical Center. The study was conducted over a period of six months, starting from September 2021 and lasting till February 2022. The patients who required IANB for any dental treatment in lower posterior teeth were divided into three groups between dental operators: Undergraduates (Interns), Graduates (House Officers), and Postgraduate trainees, having 100 cases in each group. A structured questionnaire was administered through convenience sampling to dental operators. Data was analyzed by using SPSS version 24.

Results: A total of 300 cases were part of the study. According to the results, 28% (n=84) of patients suffered from transient facial nerve palsy following IANB. Out of this 84%, 15% (n=45 of total cases) were by Undergraduates (Interns), 10% (n=30 of total cases) were caused by Graduates (Interns), and only 3% (n=9 of total) incidences happened following IANB by Postgraduate trainees.

Conclusions: The incidence of IANB-related facial nerve palsy (FNP) is comparatively more in junior dental operators, which depicts their lack of clinical experience.

Keywords: Complications, Inferior alveolar nerve block, Facial nerve palsy, Transient facial nerve palsy.

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INTRODUCTION:

In routine dental practice, local anaesthetic administration is a required step. To get the patient's participation and finish the session successfully, it is imperative to achieve enough analgesia in the operative area.[1] One of the chief methods of attaining mandibular numbness during dental procedures is the Inferior alveolar nerve block (IANB).[2] Facial nerve palsy (FNP) occasionally presents as a sequel to IANB.[1] Immediate or delayed types of paralysis can be observed starting from the instant of needle insertion until the beginning of symptoms.[1] It should be remembered that dental procedures involving mandibular anaesthesia can result in paralysis of the facial nerve.[1] Therefore, keen attention is needed while injecting the anaesthetic solution.[2,3] IANB involves positioning a needle adjacent to the mandibular foramen so that a local anaesthetic solution can be injected into the inferior alveolar nerve before this arrives to enter the mandibular canal.[4]

The reported incidence of facial palsy to IANB is approximately 20 to 25%.[5,6] Failure in the induction of profound anaesthesia is often caused by the absence of a distinct anatomic bone landmark, changes in the width and height of the ramus, and the location of the inferior alveolar nerve foramen.[5] The attainment of adequate analgesia in the operating field is essential to achieve the required cooperation with the patient and complete the session successfully. A variety of localized and systemic complications may arise from the IANB procedure. Some of the reported regional complications are the emergence of hematoma, trismus, infection, breakage of the needle, necrosis of soft tissue, persistent post-injection paresthesia, the spread of infection and ocular complications. In contrast, unintentional injection into the regional blood vessels, anaesthetic overdosage, speedy absorption, delay in the metabolism of anaesthetic

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drug or anaphylactic reaction are common systemic presentations of IANB.[7]

Facial nerve palsy, being a localized neurologic complication after inferior dental nerve block anaesthesia, can have several aetiologies, including viral, bacterial or fungal infections, trauma or unknown aetiology (Bell's palsy), and from a dental perspective, dental interventional procedures can be its culprit.[8] Dentistry-related peripheral facial nerve paralysis can arise from recurrent local anaesthetic shots, infections, or trauma while extracting mandibular third molars.[9]

The following factors can be used to explain the mechanism of facial weakness following dental procedures: direct anaesthesia to the facial nerve can cause a rapid onset while the anaesthetic agent is being injected; reflex vasospasms of the external carotid artery can cause the ischemia of the facial nerve, and dental infections may also indirectly affect the facial nerve.[1] Local anaesthetics, including vasoconstrictor drugs, may indirectly influence the sympathetic vascular reflex, resulting in an ischemic reaction leading to FNP. The needle's mechanical impact can also excite the sympathetic plexus, which may lead to FNP.[10]

Additionally, local anaesthetics can be neurotoxic and cause damage to the facial nerve. For example, procaine and tetracaine are more destructive than bupivacaine and lidocaine.[11] Moreover, alterations to a person's typical anatomy are, without a doubt, another contributor to the elevated risk of facial nerve paralysis.[1]

No matter what the underlying mechanisms of the FNP are, according to Andrew K et al., the operator is the only known variable influencing the likelihood of a successful local analgesic outcome.[12] This concludes with the rationale that the present study intends to discover and report the influence of clinical experience in terms of designation on the incidence of FNP after IANB among dental graduates which would provide the required statistics for the construction of a dentistry curriculum with greater emphasis on clinical IANB technique learning.

METHODOLOGY:

The purpose of this observational study is to investigate the incidence of transitory facial nerve palsy following IANB among Undergraduates (Interns), Graduates (House Officers), and Postgraduate trainees in the Department of Dentistry at Jinnah Postgraduate Medical Center. Approval was taken from the Institutional Review Board (IRB no: F.2-81/2019-GENL/35453/JPMC) of Jinnah Postgraduate Medical Center, Karachi. The sample size of 300 patients was calculated using OpenEpi software. Three hundred patients were enrolled in the research after the signing of written and informed consent. Both genders of dental professionals were randomly invited and selected to participate in the research.

Data was collected over the period of six months, starting from September 2021 and lasting till February 2022. The Regardless of age, gender or socioeconomic status, the patients who required IANB for any kind of dental treatment in lower posterior teeth were divided into three groups between dental operators, namely, Undergraduates (Interns), Graduates (House Officers), and Postgraduate trainees having randomly assigned 100 cases in each group. IANB was administered using a conventional technique, and patients were evaluated at an interval of 30 minutes for transient facial nerve palsy. Patients were especially screened for allergies to lidocaine (via transdermal patch test), latex allergy. the ones who had a history of systemic diseases, smoking habits and pregnancy were excluded.

Frequencies and percentages were calculated, and their correlation was assessed via Pearson Chi-Square in SPSS version 24. The questionnaire provided had two components. The first one was comprised of questions on the participant's demographic information about their age, gender, and socioeconomic standing. The next section included relevant questions about the incidence of facial nerve palsy and the designation of the dental operator administering IANB.

The identification of facial palsy was established initially via visual inspection and subsequently in detail by assessing and noting the motor functions of the facial nerve via a set of questions in which patients were asked to open the mouth, make a smiley face, to blow their cheeks and clenching their teeth. The patients were asked to rate the pain experienced during administration of IANB on a like-rt scale of 1 to 10. Score more than equal to 8 rating was considered painful.

The questionnaire was completed by the author, who was responsible for data collection. Only acute facial nerve palsy was included in this investigation. Each patient was evaluated for 60±10 minutes for the signs and symptoms of FNP, as mentioned earlier. The patients who received FNP following IANB were reassured that this is a transient occurrence and that they will return to normal within three to six hours, estimated from the time IANB was delivered.

Keeping the patient history into account, all the patients were administered MEDICAINE® Inj. (2% lidocaine hydrochloride with epinephrine 1:100,000), Huons Co., Ltd, Korea.)

RESULTS:

A total of 300 cases were divided into three groups: Undergraduates (Interns), Graduates (house officers) and Postgraduate dental trainees, with 100 cases in each group. Out of which 54% (n=162) were males while 46% (n=138) were females. Following the findings of the research, 28% (n=84) of patients suffered from transient facial nerve palsy following IANB (Fig 1). Out of them, 15% (n=45 of total cases) were by Undergraduates (Interns), 10% (n=30 of total cases) were caused by Graduates (Interns), and only 3% (n=9 of total) incidences happened following IANB by Postgraduate trainees (Figure 1). The proportions of cases showing facial palsy did differ by designation reaching

statistical significance, $X2$ (2, N = 300) = 32.44, p < 0.01.(Table 1) The odds of incidence of FNP is 8.27 times more if the dental operator is an undergraduate when compared to a postgraduate trainee. In contrast, the odds of occurrence of FNP are comparatively less, i.e., 4.33 if the IANB is administered by a graduate when compared to a postgraduate trainee.

In addition, when gender was considered for the 84 patients with FNP, it was discovered that the majority were female (56%, n=47), while the number of men was less (44%, n=37) (Table 1).

Most of the patients in which FNP happened (73 out of 84), were unable to recall anything uncomfortable or unsettling about the IANB injection, while 11 individuals had a painful IANB injection. All eleven patients with a painful IANB injection were given block anaesthesia by undergraduate dental students. Based on symptom interpretation, only 13 patients rated dysesthesia as their most problematic symptom, while paresthesia was prominent in the majority of patients (n=71)

Figure 1: Diagramatic representation of Incidence of Facial Palsy

Table 1: Summary of the Results showing Designation wise incidence.

Dental Operators	Incidence	
	Transient FNP Present (n=84) (M=37, F=47)	**Transient FNP Absent (n=216)**
Undergraduates (Interns)	15% (n=45) (M=19, F=26)	18.3% (n=55)
Graduates (House Officers)	10% (n=30) (M=13, F=17)	23.3% (n=70)
Postgraduate Trainees	3% (n=9) (M=5, F=4)	30.3% (n=91)
Overall Incidence	28% (n=84) (p < 0.01) * X^2 (2, N = 300) = 32.44, p < 0.01	

*A p-value less than 0.05 is statistically significant. M=Males; F=Females

DISCUSSION:

An essential part of routine dental practise is administering local anaesthetic. To complete the session and obtain the necessary cooperation from the patient, appropriate analgesia must be achieved in the operating area. Depending on how long it was between the time of the injection and the commencement of the symptoms, the paralysis might either be instantaneous or delayed. This article's goal is to describe cases of transient facial palsy caused by inferior alveolar nerve block patients who experienced it at intervals of 30 minutes.[1]

This study reports overall 28% prevalence of FNP which occurs as a complication of IANB administration. Being dental procedure as a causative identity, facial nerve palsy is a rare condition, and dental infections or paradental foci are mostly thought to be accountable.[13,14] Overall the total number of cases of facial palsy has been estimated to vary between 17 and 35 cases per 100,000 for all causes.[15] While in a later study, facial palsy by local anesthetic administration has reported incidence between 1:42 and 1:750,000 with multiple causative mechanisms.[16]

Vasconcelos BC et al. suggested three possible mechanisms by which nerve damage can occur, resulting in Facial Nerve Palsy (FNP), i.e., direct nerve trauma, intraneural hematoma and injury due to local anesthetic toxicity.[13] Dental work-related facial palsy can occur as acute or delayed presentation. The complication of facial nerve palsy of acute origin most commonly arises following local anesthesia administration during dental treatment, initiating the facial paresis shortly following the insertion of a local anesthetic for an IANB, which is usually followed by recovery within 12 to 24 hours.[17] About 90% complete recovery in patients with incomplete palsy has been reported,[18] while delayed facial palsy following the local anesthetic administration is uncommon.[19]

It has been reported by Thangavelu K et al., facial nerve palsy might be caused directly or indirectly by iatrogenic sources.[5] So, it can be hypothesized that clinical experience assumes a significant part in the incidence of facial palsy in dental procedures, which is supported by the results of this study. Therefore a good knowledge of anatomical structures and their orientation is very crucial for a successful and complication-free inferior alveolar nerve block (IANB).[21] According to Harini K et al., only 10% of dentistry students have an adequate understanding of the neurological consequences of IANB while managing and providing local anesthetic, whereas 60% have intermediate knowledge. Compared to this, 30% of individuals have inadequate knowledge.[22] The findings of Harini K et al. are also supported by a study by Aburas H et al., which concludes that more experience in the clinical field a dentist gains results in a lesser amount of complications, including facial nerve palsy.[23] Furthermore, considering the gender of the patients, the majority of published case reports describe facial palsies in females,[9,24-27] which is supported by the findings of this paper, which indicate a 56% incidence in females compared to 44% in men. But the results of this paper could be biased as no gender-centered randomization was aimed.

In this study, we used MEDICAINE® Inj. (2% lidocaine

hydrochloride with epinephrine 1:100,000), Huons Co., Ltd, Korea.), the main reason for choosing lidocaine was because it is an amide and there is a relatively minimal risk of allergic reaction; according to research published in North American publications, the rate of allergic reactions is around 0.7%.[28,29]

Moreover, only conventional technique for IANB administration was included in this research because the Vazirani-Akinosi nerve block and the conventional inferior alveolar nerve block techniques have been compared in multiple research; nevertheless, these investigations have produced inconsistent outcomes.[30,31]

The findings of this research provide a source for further detailed studies. It will be beneficial for designing a more clinically oriented curriculum by providing relevant statistics on IANB-related transient facial palsy. Furthermore, as the incidence of FNP was highest in undergraduate students, statistics from this paper encourage the introduction of virtual reality simulators, as presented by C G Correa et al.,[32] which could be incorporated into the undergraduate curriculum, aiding the dental students in minimizing the IANB-related FNP in their clinical practice. Limitation of time and resources, which rendered us to get ourselves limited to a small sample size, are some of the drawbacks of this study.

CONCLUSION:

Incidence of IANB-related facial palsy is more among junior dental operators depicting their lower clinical experience. Clinical expertise increases as the designation of dental operators change from Undergraduates to Postgraduate trainees. So, to minimize its incidence, dental operators must be critically taught via a comprehensive curriculum.

Limitations of the Study:

This study is limited to one institutional data. It may be possible that the demographic factors of the patients coming to the dental out-patient department where this study was conducted are the same, which can create a bias as the results will lack the diversity of the patients demographically. Moreover, the professional expertise possessed by any dental professional from different institutes may differ. Expanding the same methodology in multi-institutional data collection may eliminate this bias.

Conflict of Interest: The authors of this study agree with the conclusions drawn from this investigation and do not have any competing interests to declare.

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Authors Contribution:
Rehan Ahmad: data collection, performed data analysis, drafted the manuscript and final review
Sabeen Masood: designed the study, drafted the manuscript and performed literature search.
Jehan Alam: Supervisor, performed the critical review of the manuscript

REFERENCES:

1. Tzermpos FH, Cocos A, Kleftogiannis M, Zarakas M, Iatrou I. Transient delayed facial nerve palsy after inferior alveolar nerve block anesthesia. Anesth Prog. 2012;59(1):22– 27. doi: 10.2344/11-03.1.
2. Potocnik I, Bajroviæ F. Failure of inferior alveolar nerve block in endodontics. Endod Dent Traumatol. 1999 Dec;15(6):247-51. doi: 10.1111/j.1600-9657.1999.tb00782.x. PMID: 10825834.
3. Sweta VR, Thenmozhi MS. Facial nerve paralysis after anaesthetic usage-a review. J. Pharm. Sci. & Res. 2014;6(9):308.
4. Malamed S. 6th ed. Maryland Heights: Mosby; 2012. Handbook of Local Anesthesia; pp. 157–253. .
5. Thangavelu K, Kannan R, Kumar NS, Rethish E, Sabitha S, Sayeeganesh N. Significance of localization of mandibular foramen in an inferior alveolar nerve block. J Nat Sci Biol Med. 2012; 3:156–60. doi: 10.4103/0976-9668.101896. .
6. Quinn JH. Inferior alveolar nerve block using the internal oblique ridge. J Am Dent Assoc. 1998;129:1147–8. doi: 10.14219/jada.archive.1998.0392.
7. Blanton PL, Jeske AH. Avoiding complications in local anesthesia induction: anatomical considerations. J Am Dent Assoc. 2003; 134:888–893. doi: 10.14219/jada.archive .2003. 0288.
8. Miles PG. Facial palsy in the dental surgery. Case report and review. Australian dental journal. 1992;37(4):262-5. doi: 10.1111/j.1834-7819.1992.tb04741.x.
9. Ramoglu M, Demirkol M, Aras MH, Ege B. Peripheral Facial Nerve Paralysis Triggered by Alveolar Osteitis. J Craniofac Surg. 2015;26(4): e292-3. doi: 10.1097/SCS. 000000000000-1596. .
10. Pogrel MA, Bryan J, Regezi J. Nerve damage associated with inferior alveolar nerve blocks. J Am Dent Assoc 1995;126: 1150-5.
11. Crean J, Powis A. Neurological complications of local anaesthetics in dentistry. Dent Update. 1999;26:344–349.
12. Keetley A, Moles DR. A clinical audit into the success rate of inferior alveolar nerve block analgesia in general dental practice. Prim dent care. 2001(4):139-42. doi.org/10.1308/135576101322462174.
13. Rahman I, Sadiq SA. Ophthalmic management of facial nerve palsy: a review. Surv Ophthalmol 2007;52(2):121–44. doi: 10.1016/j.survophthal.2006.12.009. .
14. McKay J, Ford E. Anaesthesia: Pause for palsy. Br Dent J. 2016;221(1):3. doi:10.1038/sj.bdj.2016.472.
15. Misirlioglu M, Adisen MZ, Okkesim A, Akyil YY. Facial nerve paralysis after dental procedure. JOMR. 2016; 4(3):80. doi:10.4103/2321-3841.196356.

16. Zalagh M, Boukhari A, Attifi H, Hmidi M, Messary A. Contralateral facial nerve palsy following mandibular second molar removal: is there co-relation or just coincidence?. The Pan Afr Med J. 2014;18. doi: 10.11604/pamj.2014. 18.173. 3750.

17. Gaudin RA, Remenschneider AK, Phillips K, Knipfer C, Smeets R, Heiland M, Hadlock TA. Facial palsy after dental procedures–Is viral reactivation responsible?. J Cranio Maxill Surg. 2017;45(1):71-5. doi: 10.1016/j.jcms.2016.11.002. .

18. Holland NJ, Weiner GM. Recent developments in Bell's palsy. Br Med J. 2004;329:553– 557. doi: 10.1136/bmj.329.7465.553.

19. Brar RS, Kaur H, Kaur M, Mehta A. Rare Complications following posterior superior alveolar nerve block (PSANB) for tooth extraction: A report of two cases and review of literature. J Adv Med Dent Scie Res 2018;6(9):24-26. doi: 10.21276/jamdsr.

20. Gray RL. Peripheral facial nerve paralysis of dental origin. Br J Oral Surg. 1978;16(2):143-50. .

21. Al Meslet A, Aldhafeeri S, Alzahrani A. Knowledge and Awareness of Bell's Palsy Among Dentists and Dental Students in Riyadh City, Kingdom of Saudi Arabia. Microbiol Infect Dis. 2019;3(3):1-5. .

22. Harini K, Prabu D. Awareness and Knowledge of Neurological Complications and its Management while administering Local Anaesthesia among The Dental Students. Res J Pharm Technol. 2019;12(2):483-8. doi: 10.5958/0974-360X.2019.00085.4.

23. Aburas H, Al-Ali N, Al-Omair T, Al-asmari A, Al-jrais M, Al-rizqi M. Awareness and knowledge of neurological complications while administering local anesthesia among the dental professionals of Riyadh. Pediatr Dent Care. 2016;1(128):2. doi: 10.4172/2573-444X.1000128.

24. Miles PG. Facial palsy in the dental surgery. Case report and review. Aust Dent J. 1992 Aug;37(4):262-5. doi: 10.1111/j. 1834- 7819.1992.tb04741.x. PMID: 1444944.

25. Chevalier V, Arbab-Chirani R, Tea SH, Roux M. Facial palsy after inferior alveolar nerve block: case report and review of the literature. Int J Oral Maxillofac Surg. 2010;39(11):1139-42.

26. Ezirganli S, Kazancioglu HO. An unforeseen complication arising from inferior alveolar nerve block: is anemia possible? J Craniofac Surg. 2013;24(6):2178-9.

27. Jenyon T, Panthagani J, Green D. Transient facial nerve palsy following dental local anaesthesia. BMJ Case Rep. 2020;13(9).

28. Mackley CL, Marks JG, Anderson BE. Delayed-type hypersensitivity to lidocaine. Archives of dermatology. 2003;139(3):343-6.

29. Lottinger C, McNeish J. Local Anesthesia. In: Ferneini EM, Goupil MT, editors. Office-Based Maxillofacial Surgical Procedures: A Step-by-step Approach. Cham: Springer International Publishing; 2019. p. 66.

30. Prabhu Nakkeeran K, Ravi P, Doss GT, Raja KK. Is the Vazirani-Akinosi Nerve Block a Better Technique Than the Conventional Inferior Alveolar Nerve Block for Beginners? Journal of Oral and Maxillofacial Surgery. 2019;77(3):489-92.

31. Goldberg S, Reader A, Drum M, Nusstein J, Beck M. Comparison of the anesthetic efficacy of the conventional inferior alveolar, Gow-Gates, and Vazirani-Akinosi techniques. Journal of endodontics. 2008;34(11):1306-11.

32. Correa CG, Machado MAdAM, Ranzini E, Tori R, Nunes FdLS. Virtual Reality simulator for dental anesthesia training in the inferior alveolar nerve block. Journal of Applied Oral Science. 2017;25:357-66.

Original Article **Open Access**

An Assessment of Asymptomatic Bacteriuria During Pregnancy and Antimicrobial Resistance to its Common Bacterial Isolates in the Urine

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ABSTRACT:

Objective: The objective of this study is to assess asymptomatic bacteriuria during pregnancy and its antimicrobial resistance to the common bacterial isolates in the urine.

Study Design and Setting: The cross-sectional study was carried out in the Antenatal Clinic, Obstetrics and Gynaecology Unit of Avicenna Medical and Dental Hospital, Lahore, Pakistan.

Methodology: This descriptive, cross-sectional study lasted for nine months and information was collected with the help of a self-designed questionnaire using non-probability random sampling. The frequency distribution of socio-economic and demographic factors of 167 pregnant women was observed while the cultural examination was performed on urine samples of diagnosed cases of asymptomatic bacteriuria through microscopy to find out antimicrobial resistance against bacterial isolates.

Results: The prevalence rate of asymptomatic bacteriuria was 13.2%. The most common pathogen was *E. coli* followed by *Klebsiella Pneumoniae* and *Staphylococci*. Resistance of urine pathogens was observed against Ampicillin, Amoxiclav, Norfloxacin, and Piperacillin/Tazobactam.

Conclusion: *E. coli* was identified as the most predominant pathogen that showed higher resistance to Cefotaxime. History of renal stone, trimester, parity, education and low-socio-economic status were the significant factors for ASB

Keywords: Urinary tract infection, Bacteriuria, Bacterial Isolates. Anti-microbial resistance

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INTRODUCTION:

Asymptomatic bacteriuria (ASB) is defined as the occurrence of significant bacteriuria without any clinical findings. There is microbial and hormonal growth in urine during pregnancy.[1] Prevalence of ASB generally ranged from 2.5% to 10% during pregnancy. The change in prevalence rate is due to the variation in geographical region and culture that varies from country to country. Some countries such as Brazil and India showed a higher incidence rate of 12.3% and 13.2%.[2,3] The root cause of the higher incidence rate is still unknown. Pre-term labor is reported as the most common complication with ASB during pregnancy[1,2] while acute pyelonephritis is observed as the most severe complication as it could be life-threatening for foetus and mother.[3]

Early diagnosis and treatment of ASB can minimize the risk of pyelonephritis.[3,4]

Several factors are known to affect the likelihood of ASB in pregnant women. These factors include age, living standard, parity, sexual activity, past history of urinary tract infection (UTI), UTI abnormalities, maternal history, medical history, socio-economic status, and educational status. Such factors have been shown to have an association with the incidence of ASB.[4]

Bacteriuria often develops in the first few months of pregnancy and is frequently associated with a reduction in concentrating ability, suggesting an involvement of the kidney.[5] The smooth muscle relaxation and following urethral dilatation that accompanies pregnancy are thought to facilitate the ascent of bacteria from the bladder to the kidney.[6]

Most of the available research showed that bacteriuria was the only factor associated with pre-term delivery before 36 weeks of pregnancy, preterm premature rupture of membrane,

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and low birth weight. The identification of asymptomatic bacteriuria via urinalysis in the first trimester may be a predictor of adverse perinatal outcomes.[6,7] Studies have been carried out to estimate the development of risk of infection in the patients with asymptomatic bacteriuria after some urologic surgeries, but no association was found between ASB and postoperative complications among these patients. There are also some relevant facts, graded as significant in terms of prevention and screening of asymptomatic bacteriuria among patients going for urologic interventions.[7]

Asymptomatic bacteriuria and symptomatic UTI both are associated with the isolation of a specified quantitative count of bacteria in an appropriately collected urine sample.[5,8] Pregnant women with ASB increased maternal and foetal complications, and have known associated factors like increase in age, sexual activity, history of UTI before pregnancy, lower socio-economic status, several pregnancies, and lack of personal hygiene.[8]

Pathogens and the resistance to antibiotic treatment differ with respect to geographical region. *Escherichia* (*E. coli*) was observed as the most common agent identified during cultural examination.[1,4] *E. coli* has been reported as the most common agent followed by *Klebsiepneumonianiae*.[9] A fast-growing case of ASB over the last decade has shown *Klebsiella pneumonia* as the cause in the US. The prevalence of Streptococcus group B has been observed as a strong prevalent agent in large-scale studies with *E. coli* and *Klebsiella pneumonia*.[9]Antibiotic treatment considerably affects the prevalence of isolate resistance in the case of ASB during pregnancy.[10]

The main aim of this study was to observe the demographic factors that could be the cause and associated risk factors of ASB during pregnancy. With the cultural examination of urine, the major prevalence of pathogens was observed and antibiotic treatment was analysed.

METHODOLOGY:

A cross-sectional study was conducted at Antenatal Clinic, Avicenna Medical & Dental Hospital was collected. The data was collected from 167 pregnant females using a non-probability sampling technique. The study lasted for nine months (from February 2020 till October 2020). The sample size was calculated taking a confidence interval of 95% with 5% as absolute precision by using the following formula:

Sample size (n) = Z^2 1-(α)/2 (P(1-P))/d2

^{Z} 1-α/2 ^{Z} 1-α/2 = 1.96

P is the prevalence of asymptomatic bacteriuria in pregnant women in Pakistan; that is 12.4 %.[1]

$1\text{-}p$ = 1 – 0.124

d^2 = 0.05 margin of error

Substituting values for the symbols:

n = 0.41755/0.0025

n =167

The calculated sample size was observed to be 176 with nine people lost in follow-up during the nine-months study. A self-designed questionnaire based on two sections was used to gather information. The first section was based on demographic information such as age, parity, maternal history, educational status, socio-economic status, history of renal stone, and trimester. The second section listed the information collected through cultural examination. The prevalence rate of common pathogens and antibiotic-resistant was documented. In the urine sample examination, each sample was divided into two portions. One was used for microscopy and the other was kept in a cool and dry place and was used for cultural examination if the results of microscopy were found positive. The reliability of the questionnaire was tested as 70% using Cronbach alpha.

Before the data collection process, a brief explanation of the study was given and written consent was obtained from each participant. Females of age more than 35 years and with any past history of acute pyelonephritis were excluded from the study. The inclusion criteria of the participants were the females of the age group 18-35 years and who visited the antenatal clinic at Avicenna Medical & Dental Hospital during pregnancy.

The ethical approval of the study was taken from the Institutional Review Board (IRB) of the University of Lahore (Ref. No. IRB-UOL-FAHS/716/2020) before the start of the study. The descriptive of the socio-economic and demographic variables were calculated. The categorical variables were presented in the form of frequency distribution. The prevalence of ASB was observed and the chi-square test of association was applied to assess the statistically significant association of socio-economic and demographic variables with ASB at a 5% level of significance. The associated significant factors from the chi-square test of association were further assessed as to whether those were independent risk factors for ASB or not. The binary logistic regression was performed with significant associated independent factors. Results were given in the form of significant values and odd ratios. The percentage of pregnant women with various urinary pathogens isolated from their urine samples was given. Graphically and theoretically, the resistance of each antibiotic to all the pathogens was presented. Statistical Package 21.0 was used for the analysis purpose.

RESULTS:

Data collected showed that the majority of the pregnant women were 20-30 years old. The overall prevalence rate was 13.2%. Most of the pregnant women belonged to a low socioeconomic status. The results of the frequency distribution of pregnant women have been given in Table 1. Approximately 90% of pregnant women visited during the second and third trimesters of pregnancy. Nearly 9% of the women had a history of renal stone but no one was diagnosed

with ASB. The significant associated factors were taken as independent variables. The value of the estimate, standard error, significance level, and odds ratio are given in Table 2. Educational level was found as an insignificant risk factor for ASB. The illiterate group was used as the reference group. The results indicated that illiterate people were at more risk for ASB. The estimate of the coefficient was negative for parity. Multipara was used as a reference group for the factor parity. Since the coefficient is negative with an odds ratio of 0.274, pregnant women with primigravida had more chances of parity. The significance level was greater than 0.05 so parity was found to be insignificant. The coefficient of low socioeconomic status was negative with a significance level of less than 0.05. Low socioeconomic status was found to be a significant risk factor for the development of ASB. The reference group was pregnant women without low socio-economic status. The odd ratio of 0.753 showed that women with low socioeconomic status were at high risk of developing asymptomatic bacteriuria. The number of children also showed a negative coefficient with an odds ratio of 0.778. The significance level showed that the number of children was an insignificant risk factor for ASB. An increase in the number of children by 1 cause (1-0.778) % chances of developing ASB. The ASB was traced to 22 pregnant women in the total sample. Urine culture of these pregnant women was performed after the microscopy. The prevalence of ASB among pregnant women was 13.2%. E. coli accounted for 45.45% was the most dominant agent found in the urine sample. *Klebsiella pneumonia* and *Staphylococcus aureus* were observed as subsequent predominant bacteria that accounted for 18.18% as given in Table 3 Antibiotics were tested for isolated urinary pathogens to find out the resistance level if any (Figure 1). Antibiotics such as Ampicillin, Amoxiclav, Norfloxacin, and Piperacillin/Tazobactam resistance were tested for urinary pathogens. *E.coli* resistance to ampicillin was found in 62% of cases, followed by *Staphylococcus aureus* resistance in 68% of cases. *Klebsiella pneumoniae's* resistance to ampicillin was found in 78%. High resistant E.coli (80%) was found against "Cefotaxime" while Cefotaxime showed the minimum resistance (49%) against *Staphylococcus aureus*. Norfloxacin showed the highest resistance (72%) against *E. coli* and the lowest (60%) against *Staphylococcus aureus* while piperacillin showed the highest (62%) against *Staphylococcus aureus* and lowest (56%) against *Candida albicans.*

Table 1: Frequency Distribution of Socio-Economic & Demographic Factors

Variables	Categories	ASB		Total	Chi-square	p-value
		ASB	No ASB			
Age	< 20	0	12	12	2.539	0.468
	20-30	19	108	127		
	30-40	3	23	26		
	> 40	0	2	2		
	Total	22	145	**167**		
Parity	Primi-gravida	7	106	113	13.054	0.000
	Multipara	15	39	54		
	Total	22	145	**167**		
Educational Status	Literate	6	83	89	5.741	0.017
	Illiterate	16	62	78		
	Total	22	145	**167**		
Low-Socio Economic Status	Yes	13	126	139	8.684	0.003
	No	9	19	28		
	Total	22	145	**167**		
No. of Children	0	9	59	68	2.203	0.698
	1	2	16	18		
	2	7	29	36		
	3	4	41	45		
	Total	22	145	**167**		
History of Renal Stone	Yes	8	7	15	19.540	0.000
	No	14	138	152		
	Total	22	145	**167**		
Trimester	1	1	9	10	8.865	0.012
	2	3	66	69		
	3	18	70	88		
	Total	22	145	**167**		

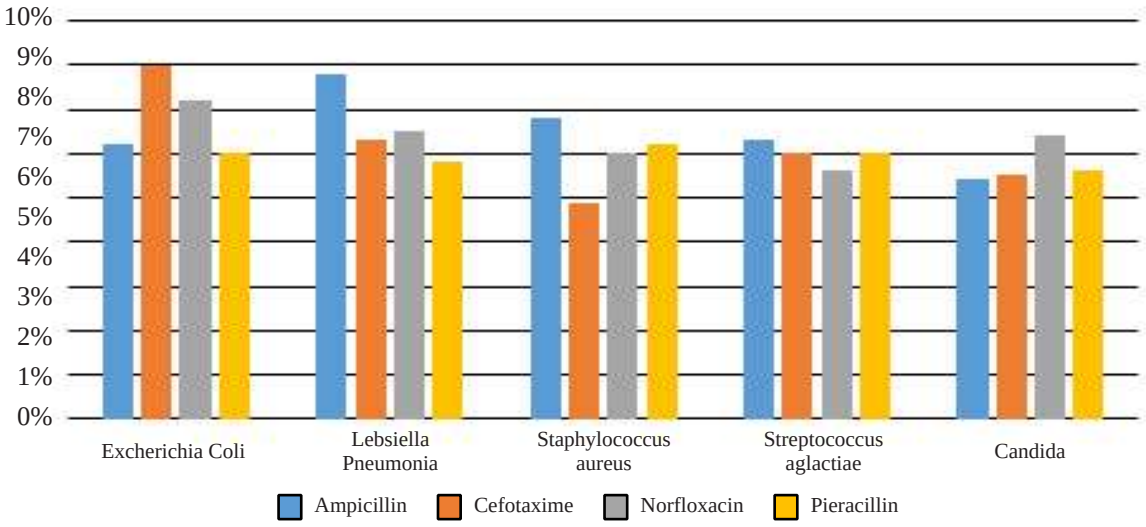
Table 2: Binary Logistic Regression for the Associated Risk Factors

Variables	B	S.E	Significance	Odd ratio
Educational Level	0.095	0.823	0.908	1.099
Parity	-1.293	0.830	0.119	0.274
Low-Socio Economic Status	-0.283	0.712	0.069	0.753
No. of Children	-0.251	0.400	0.530	0.778
History of Renal Stone	-2.636	0.694	0.000	0.072
Trimester	-1.285	0.440	0.003	0.277

Table 3: Spectrum of Urinary Pathogens isolated from urine sample of Pregnant Women with ASB

Bacteria	No. of Pregnant Women with ASB	Percentage among Pregnant Women with ASB
Escherichia coli	10	45.45%
Klebsiella pneumoniae	4	18.18%
Staphylococcus aureus	4	18.18%
Streptococcus aglactiae	3	13.63%
Candida albicans	1	4.54%
Total	22	100%

Figure 1. Resistance of Antibiotics against Urinary Pathogens



DISCUSSION:

The prevalence rate of ASB during pregnancy varied with respect to the change in culture and geographical region. The prevalence rate observed in the present study was 13.2% which was higher compared to many other studies conducted in Pakistan. A study conducted in Pakistan reported an 8.89% prevalence of ASB among pregnant females presented at IYB Headquarters Hospital Attock, Pakistan[11]. This result was slightly lower than our findings. The findings were somehow closer to another study conducted in Ethiopia where the prevalence of ASB among pregnant females was 16.9%[12]. Another study conducted in Bangladesh reported that the prevalence of ASB during pregnancy was 16.5%[13]. The same findings can be observed in another study conducted in Ethiopia where the prevalence of ASB was reported as 16.1%[14]. These studies showed the prevalence rate of ASB was slightly higher than our study. Another study in the literature reported that the prevalence was 11.5%[15]. As opposed to our results, some studies showed a prevalence rate between 4.3% and 4.8% during pregnancy.[16,17] In a study carried out in Turkey, the incidence rate of ASB in pregnant women was reported to be 8.5%[14]while the prevalence rate of ASB in pregnant women ranged from 2.5% to 10%. Similar to our findings research conducted in India has reported the prevalence of ASB as 13.2%.[3] A retrospective randomized study carried out in Israel reported the incidence of ASB as low as 2.5% among the screened 199,093 pregnant women.[18]

Most of the women diagnosed with ASB visited during the 2nd and 3rd trimesters in the present study. Similar was the case in Bulgaria where 65 women were screened with a difference in mean-age i.e., 31.3 years.[19] In our study the common age group was 20-30 years while the mean age group was reported as 28.2 and 25.33 in other studies that supported our findings.[20,21]

E. coli has been observed as the strong pathogen identified from cultural examination of urine in the present study This pathogen had also been reported in many other types of research. In one such study, *E. coli* was identified in 58.9% of cases with an incidence rate of 2.5%[18]. Another screening test isolated *E. coli* in 76.6 of the ASB cases[14]. Another study conducted in India found that *E. coli* was the most dominant and usual isolate[22,23]. In addition to *E. coli*, another dominant pathogen isolated from the urine sample in our study was *Klebsiella pneumonia* and *Streptococci*. Another study conducted in Ethiopia also observed *E. coli* as the predominant among all pathogens followed by *Staphylococcus aureus*[12]. These pathogens were also observed as dominant bacteria in large-scale studies with a low incidence rate of ASB.[14,19] Another study also observed *E. coli* as the dominant pathogen among all followed by *Staphylococcus aureus.* The study observed *E. coli* in 43.75% and the second most prevalent *Staphylococcus aureus* at *31.25%*[11] Study also concluded that there exists a prominent difference in the dominance of pathogens liable for ASB from place to place indicating the importance of urine culture to support in identifying the exact correct causative organism.[11]

Many pathogens isolated in urine have been found to be sensitive to antibiotic treatment in the present study. Screening at early stages would give useful grounds to the antibiotic treatment[1]. Some studies strongly recommended screening at an early stage of pregnancy or at the first prenatal visit at a medical center.[21] A routine screening was also suggested in those regions where the incidence rate was higher than normal.[23]

CONCLUSION:

A cross-sectional study, carried out at Gynaecology and Obstetrics Outpatient Department comprised 0–30-year-old pregnant women, most of whom were literate and belong

to a low socioeconomic class. Most of these women visited the antennal clinic in the 2nd and 3rd trimesters. The prevalence rate of ASB was found to be 13.2%. Maternal and medical history was not a significant factor for ASB. Through urine cultural examination, *E. coli* was found as the most significant pathogen followed by *Klebsiella pneumonia* and *Staphylococci.* Antibiotics such as Ampicillin, Amoxiclav, Norfloxacin, and Piperacillin/Tazobactam resistance were tested for these urinary pathogens. *Klebsiella pneumonia* was highly resistant to Ampicillin while *E. coli* had maximum resistance to Cefotaxime.

Authors Contribution:
Sana Noor: Literature search, questionnaire design, data collection and compilation
Ejaz Mahmood: Conceived the idea, Study design and concept, and Supervision
Noor Shahid: Data analysis and interpretation, manuscript writing
Arooj ul Hassan: Co-supervised the research work
Saba Noor: Data collection and compilation, Research collaboration

REFERENCES:

1. Garnizov TM. Asymptomatic bacteriuria in pregnancy from the perspective of public health and maternal health care: review and case report. Biotechnology & Biotechnological Equipment. 2016 ; 30 (3): 443-7. DOI: https://doi.org/10.1136/bmjopen-2017-021347
2. Darzé OI, Barroso U, Lordelo M. Clinical predictors of asymptomatic bacteriuria during pregnancy. Revista Brasileira de Ginecologia e Obstetrícia. 2011; 33 (8): 196-200.
3. Rajaratnam A, Baby NM, Kuruvilla TS, Machado S. Diagnosis of asymptomatic bacteriuria and associated risk factors among pregnant women in Mangalore, Karnataka, India. Journal of clinical and diagnostic research: JCDR. 2014; 8 (9): OC23. DOI: https//doi.org/10.7860/JCDR/2014/8537.4842
4. Marahatta R, Dhungel BA, Pradhan P, Rai SK, Choudhury DR. Asymptomatic bacteriurea among pregnant women visiting Nepal Medical College Teaching Hospital, Kathmandu, Nepal. Nepal Medical College journal: NMCJ. 2011; 13 (2): 107-10.
5. Wing DA, Rumney PJ, Preslicka CW, Chung JH. Daily cranberry juice for the prevention of asymptomatic bacteriuria in pregnancy: a randomized, controlled pilot study. The Journal of urology. 2008; 180 (4): 1367-72.DOI: https://doi.org/ 10. 1016 /j.juro.2008.06.016
6. Shuja S, Pario S, Muneeb A. Asymptomatic Bacteriuria in Women Presenting to Antenatal Clinic at a Tertiary Care Hospital in Karachi, Pakistan. Pakistan Armed Forces Medical Journal. 2018; 68 (5): 1138-42.
7. Pario S, Muneeb A, Shuja S. Asymptomatic bacteriuria in women presenting to antenatal clinic at a tertiary care hospital in Karachi, Pakistan. Pak Armed Forces Med J. 2018; 68 (5):1138-42
8. Acharya R. Asymptomatic urinary tract infections among pregnant women attending antenatal clinic at tertiary care hospital. Journal of Evidence Based Medicine and Healthcare. 2019; 6(14):1122-1124 DOI: https://doi.org/10.1186/1756-0500-7-155
9. Annaldasula A. A Study on Urinary Tract Infections in Pregnancy. Annals of International medical and Dental Research. 2018; 4 (2): 21-24
10. Ramos-Castaneda J, Ruano-Ravina A, Munoz-Price L, Toro-Bermúdez R, Ruiz-Londoño D, Segura-Cardona A et al. Risk of infection in patients undergoing urologic surgery based on the presence of asymptomatic bacteriuria: A prospective study. American Journal of Infection Control. 2019; 6 (2): 24-29 DOI: https://doi.org/ 10.1016/j.ajic.2019.06.024
11. Abbas N, Javaid R, Gul S. Prevalence of asymptomatic bacteriuria in pregnancy. Age (years). 2017;15(21):22-8. DOI: https://doi.org/10.2147%2FTCRM.S267101
12. Wabe YA, Reda DY, Abreham ET, Gobene DB, Ali MM. Prevalence of asymptomatic bacteriuria, associated factors and antimicrobial susceptibility profile of bacteria among pregnant women attending Saint Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia. Therapeutics and Clinical Risk Management. 2020;16:923.
13. Khanum S, Ahmed JU, Khanam. Bacterial etiology, antibiotic sensitivity pattern and risk factors for asymptomatic bacteriuria during pregnancy: experience in a tertiary care Hospital. BIRDEM Med J. 2016;6(2):79–83. DOI: https://doi.org/10.3329/birdem.v6i2.31289
14. Nisha AK, Etana AE, Tesso H. Prevalence of asymptomatic bacteriuria during pregnancy in Adama city, Ethiopia. Int J Microbiol Immunol Res. 2015l;3(5):058–63
15. Derbie A, Mekonnen D, Abate E, Tadesse S, Birku T, Biadglegne F. Bacterial isolates and their current drug susceptibility profile from urine among asymptomatic pregnant women attending at a referral hospital, northwest ethiopia. Ethiopian J Reproductive Health. 2018;10(2):1–10
16. Fatima N, Ishrat S. Frequency and risk factors of asymptomatic bacteriuria during pregnancy. Journal of the College of Physicians and Surgeons--Pakistan: JCPSP. 2006 Apr 1; 16 (4): 273-5.
17. Sheiner E, Mazor-Drey E, Levy A. Asymptomatic bacteriuria during pregnancy. The journal of maternal-fetal & neonatal medicine. 2009; 22 (5): 423-7. DOI: https://doi.org/ 10.1080/14767050802360783
18. Garnizov TM. Asymptomatic bacteriuria in pregnancy from the perspective of public health and maternal health care: review and case report. Biotechnology & Biotechnological Equipment. 2016 ; 30 (3): 443-7. DOI: https://doi.org/10.1080/13102818.2015.1114429
19. Bachman JW, Heise RH, Naessens JM, Timmerman MG. A study of various tests to detect asymptomatic urinary tract infections in an obstetric population. Jama. 1993; 270 (16): 1971-4.
20. Khattak AM, Khattak S, Khan H, Ashiq B, Mohammad D, Rafiq M. Prevalence of asymptomatic bacteriuria in pregnant women. Pakistan Journal of Medical Sciences. 2006; 22 (2): 162.
21. Wadland WC, Plante DA. Screening for asymptomatic bacteriuria in pregnancy; a decision and cost analysis. Journal of Family Practice. 1989; 29 (4): 372-7.
22. Sonkar N, Banerjee M, Gupta S, Ahmad A. Asymptomatic Bacteriuria among Pregnant Women Attending Tertiary Care Hospital in Lucknow, India. Dubai Medical Journal. 2021;4(1):18-25.
23. Tadesse S, Kahsay T, Adhanom G, Kahsu G, Legese H, G/Wahid A, et al. Correction to: prevalence, antimicrobial susceptibility profile and predictors of asymptomatic bacteriuria among pregnant women in Adigrat General Hospital, Northern Ethiopia. BMC Res Notes. 2018;11(1):798. DOI:// doi.org/10.1186/s13104-018-3844-1

Original Article **Open Access**

Helicobacter Pylori Infection and Frequency of Clarithromycin Resistance by qPCR

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ABSTRACT.

Objective: Determine the frequency of Helicobacter pylori (H. pylori) infection in our population, the response to triple-quadruple regimen and resistance to clarithromycin.

Study Design and Setting: Study design is case-series, Medicare Cardiac & General Hospital, Karachi- 2020-2021. All patients (N=110) were selected from outpatient department (OPD) of the Jinnah Medical College Hospital (JMCH) and Medicare Cardiac and General Hospital.

Methodology: Patients with nausea, abdominal pain, diarrhea and IgG positive were included, and ELISA was done for detection of H. pylori infection.. IgG negative for H. pylori and having other gastrointestinal infections were excluded from this study. Patients positive with infection were prescribed the initial triple /quadruple regimen (triple regimen therapy including Proton pump inhibitor (PPI) 20 mg, Metronidazole 400mg, Amoxicillin 250 mg or Quadruple therapy by adding Bismuth subsalicylate). In ten cases of relapse Sequential / Rescue therapy were continued after a gap of 6 weeks included PPI 20 mg, metronidazole 400mg ciprofloxacin 200mg BD or Levofloxacin 400 mg OD. The qPCR was performed for the detecting resistant to clarithromycin in patients with H. pylori IgG positive after therapy.

Result: During the follow-up, 60 (54%) cases were recovered from initial triple regimen, whereas 40(36%) cases recovered quadruple therapy and remaining 10 (7%) had clarithromycin resistance and were prescribed sequential therapy replacing clarithromycin by fluoroquinolones.

Conclusion: The study showed that majority of H. pylori infected patient in our population recovered from initial triple/quadruple regimen. The alternate option with clarithromycin resistant was sequential and rescue therapy with high eradication rate.

Keywords: *Helicobacter pylori*, triple therapy, quadruple therapy, qPCR–qualitative polymerase chain reaction, sequential therapy, ELISA (Enzyme-Linked Immunosorbent Assays)

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INTRODUCTION:

Helicobacter pylori (H. pylori) is a frequent cause of gastrointestinal infection in humans. It is a gram-negative bacterium causing serious health issues such as chronic gastritis, peptic ulcer disease and gastric cancer. Spread of

infection affects nearly half of the global population. Appropriate management of *H. pylori* with combination of antibiotics is the best preventive measure against peptic ulcers and gastritis[1]. For effective healing after initial infection, it is important to select an appropriate antibiotic to treat the infection. Appropriate treatment is most important to avoid all the serious complications and antibiotic resistance[2] which is becoming serious problem in effective eradication of this infection. In the 90s, the standard triple therapy was considered as the gold standard for the treatment of H. pylor[3].,but with emergence of antibiotic resistance, sequential and rescue therapy are also in clinical use now[4]. The prevalence of *H. pylori* infection is high, in Pakistan [4, 5, 6]. A Study carried out in Lahore, three hundred patients were infected by *H. pylori*.4 Study participants, were divided into two equal groups, one group was on clarithromycin, amoxicillin and omeprazole. The other group was prescribed triple regimen with levofloxacin replacing clarithromycin. Outcomes were better in second group with less serious adverse-effects. Conditions which increase the risk of infection include poor sanitation conditions and fast urbanization. In 2015, it was reported that global burden of *H. pylori* infection, as an attributable fraction (AF) for chronic infection and cause of non-cardia gastric carcinoma.[7]. It was reported the mode of *H. pylori* transmission is unknown, but it is thought to be mainly through the fecal-oral route. Other modes of transmission of *H. pylori* are oral-oral, water-borne transmissions, or poorly disinfected endoscopes. *H. pylori* invades the luminal side of epithelial cells of the mucosal layer of stomach[8-10]. The aim of the study is to change *H. pylori* -treatment with its management for the implementation and targeting educational management to assess the relative effectiveness. *Helicobacter pylori* infection is most carcinogenic and produces gastric adenocarcinoma. Due to the alarmingly high antibiotic resistance in *H. pylori*, gastroenterologists should change the empiric *H. pylori* treatment according to an antimicrobial susceptibility testing-guided appropriate treatment. Antimicrobial susceptibility patterns for *H. pylori* should be conducted to monitor the antibiotic resistance pattern. Antimicrobial susceptibility testing may be laborious and time-consuming, although *H. pylori* can be cultured in almost every microbiology laboratory after training is provided to the microbiologists, so that they can provide the susceptibility testing to guide the treatment of *H. pylori*. Culture of *H. pylori* and subsequent susceptibility testing take 1–2 weeks, and although it is time-consuming; however, there is to initiate the treatment without knowing the susceptibility testing results because most of the patients have had the infection for decades sometimes *H. pylori* is usually acquired in childhood.[4] Thus getting culture and sensitivity done is highly recommended offers an opportunity for "treating it right the first time". This is very important as the cure rate is highest with initial therapy if the right antibiotics are chosen, whereas after the failure of initial therapy, the bacterium will mostly likely develop drug resistance and it will become more difficult to treat. That is why it is important to develop advancements to the initial treatment to be able to treat it the first time and eradicate it permanently. Therapeutic options include clarithromycin, metronidazole, amoxicillin, tetracyclines, colloid bismuth sub citrate, ranitidine, proton pump inhibitors (omeprazole) and other antimicrobial agents' duration is from one week, ten days to fourteen days.[5,6]

The main outcome of this study was to assess the efficacy of bismuth-based regimens[5],carried out on the principles of second-line therapy rather than the specific agents used. The Quadruple and 14-day regimens were generally more successful than shorter triple therapy. A study found quinolone-based therapies of more than 10 days duration to be the most effective second-line therapy. While in recent years the efficacy of bismuth-based quadruple therapy as a second-line therapy has been clearly established, there is now substantial evidence that it is the best performing first-line therapy. Antibiotic resistance was studied and a clear and dramatic increase in resistance is noted for clarithromycin and levofloxacin; most notably, it may not be possible to support these therapies in most regions of the world much longer without testing.

METHODOLOGY:

All hundred and ten participants were selected from the OPD of Jinnah Medical College Hospital (JMCH) and Medicare Cardiac and General Hospital, after taking the history of the patients on the bases of symptoms related dyspepsia, epigastric pain, and nausea. All the patients gave written informed consent to participate in the study.

Inclusion Criteria: These patients had IgG positive on ELISA (Enzyme-Linked immunosorbent Assays) for detection of H. pylori infection.

Exclusion Criteria: Patients with other gastrointestinal symptoms were excluded from this study.Patients with positive infection were prescribed the appropriate antimicrobial regimen. In this study the therapeutic options include clarithromycin, metronidazole, amoxicillin, tetracycline, colloid bismuth sub citrate, ranitidine, proton pump inhibitors and other antimicrobial agents' duration is going to be monitored for fourteen days to check management outcome. Hundred and ten blood samples collected from Medicare cardiac & JMH Korangi campus, by serological test, Eliza and PCR. Antibiotic regimen was prescribed consisting of triple regimen therapy including Proton pump inhibitor (PPI) 20 mg, Metronidazole 400mg, Amoxicillin 250 mg. In case of resistance quadruple therapy was prescribed included PPI 20 mg, metronidazole 400mg BD, Amoxicillin 250 mg BD, Bismuth subsalicylate. In ten cases of reoccurrence Sequential and Rescue therapy were continued after a gap of 6 weeks included PPI 20 mg,

metronidazole 400mg ciprofloxacin 200mg BD or Rescue therapy includes PPI 20 mg BD, Metronidazole 400 mg BD, ciprofloxacin 200mg BD or Levofloxacin 400 mg OD.

The qPCR was performed on the patients to confirm the H. pylori positive cases. The DNA extraction with performed by using a zymogen extraction kit (cat# D 3205) following the kit protocol. The DNA samples were amplified with qPCR (SLAN Instrument) amplification of the H. pylori gene fragment with slightly modification the qPCR was performed with the primer sequence 5'-AGATGGGAGCTGTCTCAACCAG-3' as forward primer and the reverse primer 5'-TCCTGCGCATGATATTCCC-3' (Integrated DNA Technologies, Inc., Coralville, Iowa) The total volume of master mix was 25ìl for qPCR. The master mix including 10 µl, (ABM One Step Bright Green q PCR kit G891), 2.5ìl set of primer, 5ìl extracted DNA and nuclease-free water to make the volume 25 ìl. The thermal cycle was programmed was pre-denaturation at 95°C for 10min, following with 40 cycles, denaturation at 95°C for 15 second, annealing at 60°C for 1 minute.

The ethical consideration was approval from ethnic research committee (ERC) of Jinnah Medical and Dental College (Protocol #. 00043/20).

RESULTS:

The patients included in study with general characteristics having the symptoms of dyspepsia and epigastric pain. In this study 50 % were the male and 60 % female with the age range between 20-70 years, with low to middle socioeconomic status as shown in table 1. Antibiotic regimen prescribed to the patients with *H. pylori* positive. The triple regimen therapy included Proton pump inhibitor (PPI) 20 mg x bid, amoxicillin 500 mg x tds, clarithromycin 500 mg x bid for fourteen days and were asked to come for follow-up. In 50 patients, prescribed quadruple therapy having PPI 20 mg, metronidazole 400mg bid, amoxicillin 250 mg bid, Bismuth subsalicylate showed complete recovery on follow-up. The n=10 with relapse, were prescribed sequential therapy. During time period 10 patients showed no response with clarithromycin and again IgG was performed and it was still positive and on performing the qPCR, *H. pylori* strain was observed the resistant pattern as shown in figure 2(a, b, c, d). The rescue therapy was prescribed that includes PPI 20 mg, metronidazole 400 mg, ciprofloxacin 500mg or levofloxacin 400 mg twice daily. On follow-up again the *H. pylori* antibodies were performed and it was noted that IgG – negative.

The qPCR was performed on the patients to confirm the H. pylori positive cases following the above-mentioned protocol. After the analysis curve and cycle threshold (Ct) value is noted as shown in figure 1and table 2. The lower Ct value is reported as positive and the Ct value is reported negative for H. pylori Figure 1 shows the positive cases which were identified on their low Ct (Cycle Threshold) value, and negative cases are identified on their high Ct (Cycle Threshold) value of *H. pylori* with qPCR. *This figure is s generated when qPCR gives the result and Ct value Table 2: shows the Cycle threshold (Ct) value of the positive patients with *H. pylori* infection. The highlighted with red shows positive cases.

After diagnosis with qPCR, the positive cases were given treatment. The first lineantibiotic regimen prescribed consisting of triple regimen therapy including proton pump inhibitor (PPI) 20 mg x bid, clarithromycin 500 mg x bid, amoxicillin 500 mg x tds. The second line quadruple therapy by including bismuth subsalicylate included after two weeks in these [n=40 (36%)] patients with symptoms. All the (N=110) cases were monitored, only [n=10(7%)] patients were found to be resistance to initial therapy were prescribed sequential therapy after a gap of 6 weeks included PPI 20 mg x bid, metronidazole 400 mg x tds`ciprofloxacin 500mg x bid.The medication was stopped for some time and again the samples were collected from these patients and this time RNA was isolated by using zymogen RNA extraction kit (cat# R1055) following the kit protocol. The qPCR was performed to identify the reason for the relapse by using type specific primer sequence of Clarithromycin resistant strain of H. pylori, 23S rRNA gene shown in table 3. The qPCR was performed on blood sample of the patients having relapse of infection due to antibiotic resistance. The qPCR protocol with some modification was performed by making total volume of reaction 30 ìl including qPCR master mix 10 µl, enzyme mix 1ìl (ABM One Step Bright Green q PCR kit G891), all the upstream primers 2 ìl, each, common downstream primer 2 ìl, extracted RNA 5ìl and volume was adjusted with nuclease-free water. The thermal cycle was programmed for cDNA synthesis at 42°C for 15min, pre-denaturation at 95°C for 10min, denaturation at 95°C for 15 seconds, annealing at 60°C for 1 minute for 45 cycles. The result was observed as shown in figure 2 with cycle threshold (Ct) value

Table 1: General characteristics of *H. pylori* infected patients

Variables	*H. pylori* **infected patients N= 110**	**Percentage**
Gender M:F	50:60	
Age	20-70 years	
Low /Middle class	110	100%
Dyspepsia	100	90%
Epigastric Pain	110	90%
Nausea	55	50%
Diarrhea	45	40%
Hematemesis & Malena	0	0

Figure1: Shows the positive cases which were identified on their low Ct (Cycle Threshold) value, and negative cases are identified on their high Ct (Cycle Threshold) value of *H. pylori* with qPCR

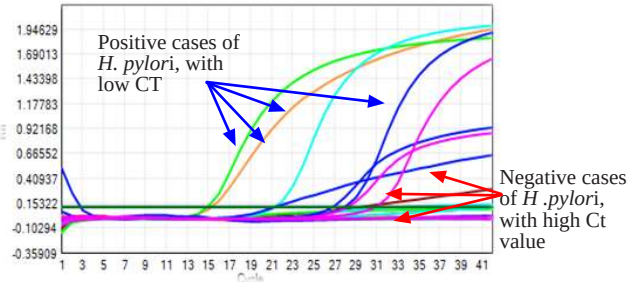


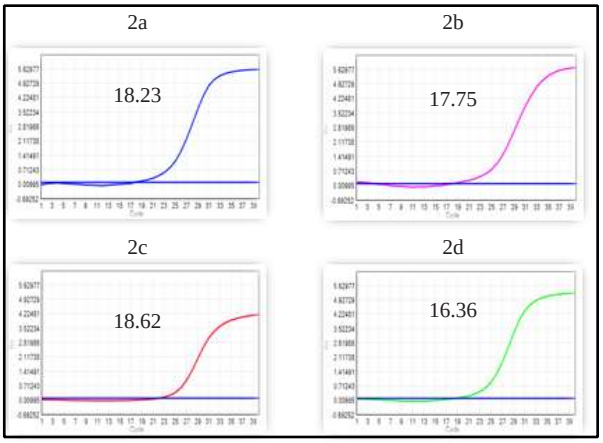
Table 2: shows the Cycle threshold (Ct) value of the positive patients with *H. pylori* infection. the highlighted with red shows positive case

Well	Project	Sample Name	Tube Name	Channel	Target	Ct Value
A1	*H. pylori*	S1	g1	1	sample	30.87
B1	*H. pylori*	S2	m1	1	sample	27.92
C1	*H. pylori*	S3	m2	1	sample	21.25
D1	*H. pylori*	S4	m3	1	sample	14.88
E1	*H. pylori*	S5	m4	1	sample	15.26
F1	*H. pylori*	S6	m5	1	sample	15.5
G1	*H. pylori*	S7	m6	1	sample	29.35
H1	*H. pylori*	S8	m7	1	sample	29.58
A2	*H. pylori*	S9	g2	1	sample	13.21
B2	*H. pylori*	S10	m2	1	sample	21.35
C2	*H. pylori*	S11	C5	1	sample	22.45
D2	*H. pylori*	S12	C6	1	NC	No Ct

Table 3: Primer sequence of information for the *H. pylori* 23S rRNA gene used for resistant with Clarithromycin

Primers	Sequence
	5'-CTACCCGCGGCAAGACTGA-3'
G upstream primer	5'-CTACCCGCGGCAAGACTGG-3'
C upstream primer	5'-CTACCCGCGGCAAGACTGC-3'
G upstream primer	5'-CTACCCGCGGCAAGACGTAG-3'
Common downstream primer	5'-ATAGGTGGGAGGCTTTGAAGTA-3'

Figure 2: a b c and d show the individual graph spikes of the resistant strain of the *H. pylori* with Clarithromycin



DISCUSSION:

Helicobacter pylori has been the causative organism for chronic gastritis, gastric /duodenal ulcers and the most serious outcome of this infection is gastric adenocarcinoma. After contact with *H. pylori* patient exhibits IgA, IgG and IgM antibodies. IgG antibody is detected (*Emproimmun Seekamp.31.23560*) in few weeks and remains in the serum for long time. *H. pylori* infection has serious complications such as duodenal ulcer and gastric cancer[7]. Thus, appropriate treatment is most essential to avoid such serious complications. The cause of *H. pylori* has been found as above fifty percent in undeveloped countries compared with nearly thirty five percent in developed countries and globally noted that 43% in females and 46% in males. The prevalence of infection in adults (=18 years) was significantly higher than in children[11], In our study females effected were 60 as compared to males 50. The high incidence of *H. pylori* is large in cities like Karachi, antibiotic resistance to clarithromycin was detected in 10 (7%) patients.

The importance of various approaches for the diagnosis of *H. pylori* and antibiotic therapy-based management is effective. The rate of recovery is greatest with initial therapy when right antibiotics have been prescribed, and the failure of initial therapy will mostly likely be due to the development of antibiotic resistance by the bacteria. Ierardi E et al 12, 2017 reported the molecular diagnosis has been used for the detection of *H. pylori* with evaluation of the virulence factors and antibiotic sensitivity. In our study out of total one hundred and ten patients having tested IgG positive for *H. pylori* were initially prescribed the triple regimen, 60 (54%) cases recovered completely, resistance or recurrence of infection 40 (36%) cases were prescribed quadruple regimen, sequential regimen prescribed 10 (7%).

H. pylori infection frequency in Pakistan is high 4,5,13 maybe due to large number of family members living together. The modification for using sequential regimen [14,15,16 17,18] showed beneficial therapeutic strategy for the management of H. pylori infection in clinical practice. The initial therapy includes triple regimen including proton pump inhibitors, clarithromycin, amoxicillin. The outcome of clarithromycin resistance has been reported worldwide[16]. Antibiotic resistance is a major problem in effective treatment to *H. pylori* infection, thus the initial triple regimen consisting of clarithromycin, amoxicillin, proton pump inhibitors are not that effective [18,19 20]. In this study resistance to initial therapy was high and recovery rate was 54% only and recovery from quadruple therapy was increase by 36%. The sequential therapy was prescribed to increase recovery rate. The triple therapy, quadruple therapy, sequential therapy and regimens containing fluroquinolones such as levofloxacin are routinely used [21, 22,23]. The continuous rise of *H. pylori* on secondary antimicrobial resistance, in particular to clarithromycin. Some patients on sequential therapy was carried out for either ten days or two weeks on esomeprazole

40 mg and amoxicillin 1 g for 7 days followed by esomeprazole 40 mg, clarithromycin 500 mg and tinidazole 500 mg for 7 days, all given twice daily. The efficacy of lansoprazole, bismuth, levofloxacin, and amoxicillin therapy compared to bismuth metronidazole tetracycline (BMT) quadruple therapy for second-line treatment of *H. pylori*. Studies found that sequential and hybrid therapies have found to be better eradication rate [24 , 25] in their studies showed triple and quadruple regimens patients with no compliance [2,25,] In study done in Korea[18], antibiotic resistance to clarithromycin has been reported 15%. Resistance against both clarithromycin and metronidazole reported was 8.6%. In our study 75% of first-line treatment is successful and whereas the participate achieved successful eradication with second-line treatment. The multidrug resistance is increasing, and standard triple therapy (STT) is no longer acceptable as first-line option eradication for *H. pylori* [14, 19] Similarly, our study has reported effectiveness consistent therapy of clarithromycin and metronidazole up to 89% and recurrence in 11% patients who were prescribed sequential and rescue therapy.

CONCLUSION:

The study was conducted to diagnosis and management of regimen to eradicate antibiotic resistant for *H. pylori.* The main challenge in treatment of *H. pylori* is resistance, which reduces the eradication by prescribed antibiotic regimens. Combination antibiotic therapy has been highly beneficial regimen for eradicating of antibiotic resistant strains of *H. pylori*. It is also concluded the importance of diagnosis of *H. pylori* by using different diagnostic tools before the treatment and on follow-up comparing with consistent guideline and new recommendations as well as the sensitivity pattern of the drug clarithromycin should be monitored in patient's detection with clarithromycin resistant *H. pylori* infection.

Authors Contribution:
Samia Perwaiz Khan: Constructing an idea or hypothesis for research and/or manuscript, Taking responsibility in logical interpretation and presentation of the results
Rubina Ghani: Planning methodology to reach the conclusion, Taking responsibility in the construction of the whole or body of the manuscript
Safia Izhar: Organising and supervising the course of the project or the article and taking the responsibility
Ajeet Kumar: Biological materials, reagents and referred patients
Ambreen Irshad: Taking responsibility in this necessary function
Shaista Emad: Reviewing the article before submission not only for spelling and grammar but also for its intellectual content.
Aemen Moeen: Taking responsibility in execution of the experiments, patient follow-up, data management and reporting
Ayesha Abbasi: Taking responsibility in execution of the experiments, patient follow-up, data management and reporting
Maham Sattar: Taking responsibility in execution of the experiments, patient follow-up, data management and reporting
Syed Sohaib Hasan: Taking responsibility in execution of the experiments, patient follow-up, data management and reporting

REFERENCES:

1. Fallone CA, Moss SF, Malfertheiner P. "Reconciliation of recent Helicobacter pylori treatment guidelines in a time of increasing resistance to antibiotics." Gastroenterology. 2019 ;157(1):44–53. DOI: 10.1053/j.gastro.2019.04.011
2. Thung I, Aramin H, Vavinskaya V, Gupta S, Park JY, Crowe SE, Valasek MA. Review article: the global emergence of Helicobacter pylori antibiotic resistance. Alimentary Pharmacology and Therapeutics, 2016: 43(4):514–33. doi: 10.1111/apt.13497
3. Godersk, K., Agudo Pena, S., and Alarcon, T.;"Helicobacter pylori treatment: antibiotics or probiotics". Appl Microbiol Biotechnol. 2018:102:1–7 DOI: 10.1007/s00253-017-8535-7
4. Latif S, Akhter N, Amjed S, Jafar J, Saleem B, et.al. Efficacy of standard triple therapy versus Levofloxacin based alternate therapy against Helicobacter pylori infection. Journal Pakistan Medical Association (JPMA); 2018: 68: 1295-1299.
5. Mehmood K, Awan AA, Muhammad N, Hasan F, Nadir A. Helicobacter pylori prevalence and histopathological findings in dyspeptic patients. Journal of Ayub Medical College Abbottabad.; 2014: 26(2):182-5.
6. Hooi, JKY, Lai WY, Ng WK, Suen, MMY, Underwood FE, Tanyingoh, D et al. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. Gastroenterology .2017; 153: 420–429.
7. Plummer , M. , Franceschi, S , Vignat, J, Forman, D., Martel, C, Global burden of gastric Cancer attributable to Helicobacter pylori Int J Cancer. 2015; 136(2):487-90. DOI: 10.1002/ijc.28999
8. Samy W., Elnemr GM, Issa LF and Sedik W. "Prevalence of Helicobacter Pylori Infection and its Correlation with Complete Blood Count Parameters in Adult Males at Taif City, Saudi Arabia". SAS J. Med. 2016: Volume-2; Issue-3, p-49-54.
9. Zamani M, Ebrahimtabar F, Zamani V, Miller WH, Alizadeh-Navaei R, et.al; Systematic review with metanalysis: worldwide prevalence of Helicobacter pylori infection. Alimentary Pharmacology & Therapeutics. 2018: 47(7): 868–76, DOI: 10.1111/apt.14561
10. Nakamura S, and Matsumoto T. "Helicobacter pylori and gastric mucosa-associated lymphoid tissue lymphoma: recent progress in pathogenesis and management." World Journal of Gastroenterology (WJG). 2013:7;19(45):8181-7, doi: 10.3748/wjg. v19.i45.8181.
11. Bang CS, Lim H, Jeong HM, Shin WG, Choi JH, Soh JS. Amoxicillin or tetracycline in bismuth-containing quadruple therapy as first-line treatment for Helicobacter pylori infection. 2020; Gut Microbes, 11 ; 5:1314-1323, DOI: 10.1080/ 1949 0976.2020.1754118
12. Ierardi E, Giorgio F, Iannone A, Losurdo G, Principi M, et.al.; Noninvasive molecular analysis of Helicobacter pylori: is it time for tailored first-line therapy? World Journal of Gastroenterology. 2017: 23:2453–2458, doi: 10.3748/wjg. v23.i14.2453
13. Rasheed F, Ahmad T, Bilal R." Prevalence and risk factors of Helicobacter pylori infection among Pakistani population. Pakistan Journal of Medical Sciences.:2012: 28(4):661-665.
14. Kim SY, and Chung JW. "Best Helicobacter pylori Eradication Strategy in the Era of Antibiotic Resistance. Antibiotics (Basel)."; 2020: 23;9(8):436. doi: 10.3390/antibiotics9080436.

15. Gasparetto M, Pescarin M, Guariso G. "Helicobacter pylori eradication therapy: current availabilities." ISRN gastroenterology. 2012: Volume 2012, 8 doi:10.5402/ 2012/ 186734.

16. Kageyama C, Sato M, Sakae H, Obayashi Y, Kawahara Y , et.al.; "Increase in antibiotic resistant Helicobacter pylori in a University Hospital in Japan." J of infection and drug resistance. ; 2019: 12; 597-602. doi: 10.2147/IDR.S196452

17. Fasciana T, Di Carlo P, Jouini A, Di Giulio M.. "Helicobacter pylori: infection and new perspective for the treatment." Canadian Journal of infectious diseases and Medical Microbiology; 2019: 2 pages , doi.org/10.1155/2019/9431369.

18. Park JY, Shin T-S, Kim J-H, Yoon HJ, Kim BJ.et.al. "The Prevalence of Multidrug Resistance of Helicobacter pylori and Its Impact on Eradication in Korea from 2017 to 2019: A Single-Center Study." Antibiotics; 2020: 9(10), 646; doi:10.3390/antibiotics9100646.

19. Hwang TJ, Kim N, Kim HB, Lee BH, Nam RH, et.al. "Change in antibiotic resistance of Helicobacter pylori strains and the effect of A2143G point mutation of 23S rRNA on the eradication of H. pylori in a single center of Korea." J. Clin. Gastroenterol.; 2010: 44, 536–543. DOI: 10.1097/ MCG. 0b013e3181d04592

20. Qureshi NN, Gallaher B, Schiller N.L "Evolution of amoxicillin resistance of Helicobacter pylori in vitro: characterization of resistance mechanisms." Microb. Drug Resistance.; 2014: 20(6):509–16. doi:10.1089/mdr.2014.0019.

21. Cao Z, Chen Q, Zhang W, Liang X, Liao J, et.al. "Fourteen-day optimized levofloxacin-based therapy versus classical quadruple therapy for Helicobacter pylori treatment failures: a randomized clinical trial". Scandinavian journal of gastroenterology; 2015. 50(10):1185–90. doi:10.3109/ 0036-5521 .2015.1037345.

22. Gisbert JP, Romano M, Gravina AG, Solis-Munoz P, Bermejo F, et al. "Helicobacter pylori second-line rescue therapy with levofloxacin- and bismuth-containing quadruple therapy, after failure of standard triple or non-bismuth quadruple treatments."Alimentary pharmacology & therapeutics. 2015:41(8):768–75, doi:10.1111/apt.13128.

23. Liou JM, Chen C-C, Lee Y-C, Chang C-Y, Wu J-Y, et.al. "Systematic review with meta-analysis: 10- or 14-day sequential therapy vs. 14-day triple therapy in the first line treatment of Helicobacter pylori infection." Alimentary pharmacology & therapeutics.; 2016: 43(4):470–81. doi:10.1111/apt.13495.

24. Wang B, Wang Y-H, Lv Z-F, Xiong H-F, Wang H, et.al. "Review: efficacy and safety of hybrid therapy for Helicobacter pylori infection: a systematic review and meta-analysis. Helicobacter. 2015:20(2):79–88. doi:10.1111/hel.12180.

25. Zullo A, Fiorini G, Scaccianoce G, Portincasa P, De Francesco V, et.al. "Sequential therapy for First-Line Helicobacter pylori eradication: 10- or 14-Day Regimen?" Journal of Gastrointestinal and Liver Diseases; 2019: Vol. 28 No 1: 11-14. doi.org/10.15403/jgld.2014.1121.281.hpy

Review Article **Open Access**

Drug Resistance due to Elaboration of Beta Lactamases and the Role of CTX-M in Enterobacteriaceae

Rida Sohail, Yasmeen Taj, Luqman Satti, Shaista Bakhat

ABSTRACT:

The *Enterobacteriaceae* family are the most common pathogens associated with hospital and community acquired infections worldwide. These bacteria are treated with broad spectrum antibiotics especially 3rd generation cephalosporins. Over the period of time due widespread and rigorous use of these medications, *Enterobacteriaceae* has developed antibiotic resistance (AMR). Among all, the most compelling antibiotic resistance mechanism is production of β-lactamases enzymes by this microorganism. Over the course of time β-lactamase has evolved more than 1300 distinct enzymes. Amongst these most deleterious is extended spectrum beta lactamases (ESBL). ESBL producing *Enterbacteriacaeae* are responsible for a high number of deaths worldwide. These enzymes are considered challenging as they are difficult to be identified in the laboratory wShich cause delay in diagnosis and administration of appropriate antimicrobial therapy. The coexistence of ESBL with other antibiotic resistance gene is another therapeutic challenge rendering empirical antibiotic treatment ineffective.

Key words: *Enterbacteriacaeae*, AMR, ESBL, CTX-M

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INTRODUCTION:

Antibiotic resistance is a subject under constant evaluation, and multiple researches and new data addresses this problem every day. Resistance to β-lactam antibiotics like penicillin and cephalosporin is due to the elaboration of β-lactamase enzymes, which are responsible for degrading β-lactam drugs and have been assessed from different perspectives including dissemination and classification. These β-lactam drugs are bactericidal as they block the formation of Ala-Ala dimer required for the formation of bacterial cell wall peptidoglycan layer. β-lactams are similar to penicillin binding proteins (PBP) that mediate the cross-linking processes of peptidoglycan synthesis of bacteria. In the presence of β-lactam drugs this processes of cross-linking doesn't initiate. The constant chemical stress against these β-lactam drugs results in genetic alternation within the bacterial cell which concludes with the elaboration of â -lactamase enzymes. These enzymes thus break the beta-lactam ring of the incoming drug, ensuring bacterial cell propagation and survival. β-lactamases have been used as a model to study the enhanced evolution following Darwinian principle where the huge burden of antibiotics use allows the existence of the fittest.[1] The constant pressure due unwarranted use of antibiotics has resulted in mutations which altered the genome of bacteria so much, that targeting them has become impossible. Since the 1980s there has been a substantial rise in the number of these enzymes especially class A and D.[2] β-lactamases which include the extended-spectrum-β-lactamases (ESBL's) can degrade broad-spectrum Cephalosporins (such as Monobactams, Cefepime, Ceftriaxone and Cefotaxime) but are inhibited by Ceftazidime; this is an alarming situation.[3-4] Ambler's classification is on the basis of amino acid homology and divides the enzymes in four groups (A-D). Group A, C and D proteins shows similar folds and include an amino acid serine which is essential for the founding of an acyl–enzyme complex with the β-lactam resulting in its hydrolysis. Group B is metalloproteinase which has one or two zinc ions. These groups have specific enzyme families. Class A have TEM (Temoniera), SHV (sulf-hydryl variable) these enzymes are mostly responsible of ampicillin and penicillin resistance [5], CTX-M (cefotaximases-munich)[6] and KPC (*Klebsiella pneumoniae* carbapenemase)[7] ; NDM(New Delhi metallo-beta-lactamase) and VIM (Verona integron-borne metallo-β-lactamase (class B); and CMY (cephamycin-hydrolyzing β-lactamase) and ADC (Acinetobacter-derived cephalosporinase) class C. [8] Class D enzymes are all termed

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oxacillinase (OXA) responsible for high hydrolytic activity against Cloxacillin and Oxacillin. [9-10] CTX-M β-lactamases are thought to be the prototype in development of resistance in microorganism against antibiotics.[11] Integration of various blaCTX-M genes originating from various kind of Kluyvera has resulted different CTX-M clusters.[12] In Silico analysis and TREE VIEW program (http://taxonomy.zoology.gla.ac.uk/rod/treeview.html), based on a multiple sequence alignment of the publicly available CTX-M sequences(http://www.lahey. org/Studies/) shows that these events have happened at least nine stretches resulting in CTX-M-1 cluster, CTX-M-2 and CTX-M-9 clusters and CTX-M-8 and CTX-M-25 clusters. [13] Each cluster has been further divided in to groups and subgroups based amino acid similarity. The most prominent amongst these clusters are Group 1 and Group 9. Within these groups the CTX-M15, CTX-M-3 and CTX-M-14 are the most widespread and rapidly emerging in humans and well as in the animals. CTXM-15, the most prominent and commonest CTX-M enzyme is a derivative of CTX-M-3, which belongs to Amblers group A and cluster 1. The structural analysis of the enzymes suggest that single amino acid mutation can change the entire hydrolytic activity of the enzyme against a drug. For example the CTX-M-15 varies from its cluster 1 enzyme by single point mutation. This alternation marks increased CTX-M-15 enzymatic activity against Ceftazidime. This hydrolytic enhancement is not demonstrated by any other CTX-M enzyme.

These new genetic variants harbor mobile genetic elements such as insertion sequences like transposons and class 1 integrons.[14] The acquisition of bla CTX-M genes from the environment on these genetic elements could have been a random incident. However β-lactam selective force applied by excessive use of Cefotaxime and Ceftazidime has triggered mutations leading to modification of different clusters. Infiltration and worldwide dissemination of CTX-M producing organisms are the result of the designated "epidemic resistance plasmids" harboring resistance and high-risk virulent clones.[15] Amalgamation of these factors including co-selection of resistance element within CTX-M harboring bacteria which also produces Carbapenemases is alarming. The processes of co-selection is when a single resistant gene mediates resistance against all other drugs. This may be true as all the antibiotic resistance gene resides on the same plasmid.

The TEM and SHV ESBLs dominant in 1980s and 1990s scenario were mainly linked with nosocomial infections associated with *Klebsiella pneumoniae* and *Escherichia coli* whereas CTX-M were less dominant.[10] . However recently this epidemiology has drastically changed and now CTX-M has become the most prevalent beta-lactamases. Although first revealed in 1989, the ESBL CTX-M enzymes did not achieve dominance over other enzymes till 21th century when increased dissemination of these enzymes were detected.[16-17] They were not only restricted to nosocomial infections but disseminated is community with *E. coli* being the most prominent pathogens elaborating these enzymes.[18]

This review article is searched through PubMed, Google, and Google Scholar engine with several key words like β-lactamases, Enterobacteriaceae *salmonella typhi*, XDR, and CTM genes. A total of 70 articles were critically analyzed from 2001-2021. The data was collected and processed within six months.

1. Epidemiology of CTX-M β-lactamase-producing bacteria:

The CTX-M was present in enterobacters before cephalosporin's being dominant treating options in healthcare. Although CTX-M advent was appreciated in 1980s, its prominence become recognizable in the year 2000. Studies over the last decade have shown that CTX-M enzymes are the most dominant ESBL enzymes in *Enterobacteriaceae* .[19-20] This is a consequence of the surprising spread of the blaCTX-M gene within mobile genetic elements inside susceptible clones.[22-24] In addition there is a co-existence with other antibiotics including Aminoglycosides and Fluoroquinolones.[25-26] These isolates exhibit decrease Ciprofloxacin susceptibility (DCS, MIC value 0.38mg/L) and Luminex based assay to detect mutations in quinolone resistant determining regions (QRDR) and plasmid mediated quinolone resistant gene (PMQR) reveal that DCSs was linked with the single mutation in residue ser83 of gyrA gene. This is one of the prominent genetic elements among *salmonella typhi* (*S.* Typhi) exhibiting DCS.[27]

Among the CTX-M family, the CTX-M-14 and CTX-M-15 are the most prevalent in the human, animals and environment.[28-29] In this scenario CTX-M can be distinguished into various phases. The first phase comprises of different CTX-M β-lactamases in diverse geographic areas and these events may have happened until the mid of the 1990 decade. The second phase was marked by the appearance of CTX-M-3, CTX-M-9, CTX-M-14, and CTX-M-15 enzymes and these events might have occurred over decade ending to 2000. The third phase after 2000 is noted by the worldwide dissemination of these lactamases. The first report identified Cefotaxime resistance but Ceftazidime susceptible, was strain of *E.coli* isolated from otitis media specimen of four month old child in Munich Germany.[30]

Up till now the most disseminated CTX-M enzymes globally have been CTX-M 15 followed by CTX-M 14. These two enzymes have enhanced degrading potential and increased MIC's against Ceftazidime, an antibiotic which is not inhibited by other CTX-M family enzyme.

Recently, a new variant of CTX-M-15 has emerged, which has received incredible attention. This enzyme is CTX-M-33 which has decreased degrading activity against Ceftazidime but on the contrary increased hydrolytic activity against Carbapenams e.g. Meropenams. The increased use of Carbepenams against resistant 3rd generation

Cephalosporin's has resulted in the emergence of these strains. et al, 2019 has identified that this increase hydrolytic activity is due to point mutation which has altered amino acid sequence from serine-to-asparagine. [59]

2. Penetration and globalization of CTX-M enzymes all over the world: The worldwide expansion of CTX-M-1 cluster was represented with growing new variant over the 1990s. For example, CTX-M-10 was primarily found in the region of Mediterranean (Spain and France[10-31] and where the CTX-M-15 first found in 1999 in *Enterobacteriacea* in New Delhi, India [32] but nowadays reported from all around the world. These modifications are due to amino acid substations which are reported to have been developed from common ancestors. [33-34]

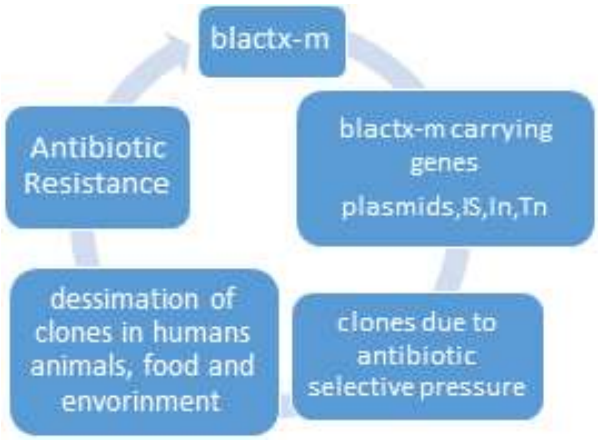
The CTX-M-15 spread in United Kingdom after it was first reported and the isolates were linked to *E.coli*.[35-36] International travel and immigration added to the speedy appearances and spread of CTX-M enzymes all over the world.[37-38] This has been recently proved with Carbapenemases in particular with NDM-1 metallo-β-lactamase producing pathogens.[39-40] However the existence of CTX-M enzymes in animals and food merchandises that are moved among different countries have proposed the likely paths for spread and dispersion. [41] Moreover this rapid dissemination has also been attributed to presence of blaCTX-M of plasmid and transposons, which confer rapid transfer of resistant elements not only within the specie but also to any bacteria it comes in contact to.

Although the global prevalence of CTX-M family is not well documented especially from developing areas making estimation of prevalence challenging and complex, published articles from Africans and Asian countries indicate rapid increase in the prevalence of this enzyme. African countries data demonstrate increase in prevalence to 13.6% within two years' time where as 95.5% isolates were positive of CTX-M in 2018 from Ethiopia. Compared to these similar findings among clinical Enterobacteriaceae isolates with prevalence rates of 91% in Brazil[60], 80.3% in Germany [61] and 79% in Switzerland [62] have been documented. A nationwide survey in china indicated 91% ESBL producing bacteria harbored CTX-M. European data from nine different countries also suggest that the most common ESBL is CTX-M which was found to be 66.4%.

3. CTX-M enzymes in bacteria other than *Enterobacteriaceae*:

CTX-M enzymes were first reported in *E. coli, K. pneumonia* and other nosocomial infection associated bacteria like *Acinetobacter, Serratia etc,* but later begin to be reported in other Enterobacteriaceae as well. This was the result of chromosomal changes which induced AmpC in Enterobacteriaceae spp, *Citrobacter* species, *Serratia marcescens*, *Enterobacter* species and *Morganella morganii* species enabling these organisms to degrade oxy-imino-cephalosporins. [16, 42-43]

Figure 1: Cycle of global dissemination of CTX-M ESBL



The first CTX-M enzymes reported in *Pseudomonas aeruginosa* from a patient of cystic fibrosis sputum sample but still presences of CTX-M enzyme in non-fermenting rods is not common.[44] This point may be the result instability of plasmids carrying these enzymes. *Vibrio* spp. or *Aeromonas* spp. isolates with CTX-M enzymes have also been reported.[45,46]

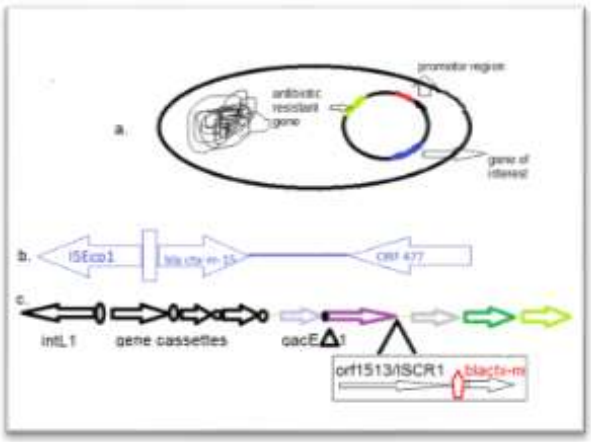
4. Foundation of the blaCTX-M genes: According to phylogenetic trees analysis the CTX-M β-lactamases can be categorized into five major clusters. Usually each cluster can be allied to chromosomal bla genes in various *kluyvera spp*, which are present in normal human intestinal floral but at very low numbers, and is a saprophytic and an opportunistic pathogen. The enterobacter captured the blaCTX-M gene on the plasmids probably from the chromosomal blaCTX-M of *kluyvera*. Also *kluyvera* has been sporadically linked with human urinary tract skin and soft tissue infections.[47] They are habitually present in the environment in water, sewage, soil, food products and animals [48-49]

5. Evolution and diversification of CTX-M β-lactamases: Presently higher than 60% of the isolates harboring CTX-M exhibit resistance towards Cefotaxime and Ceftazidime at the same time. Although the first report of CTX-M harboring resistance towards Cefotaxime but were not able to hydrolyze Ceftazidime. It can be therefore presumed that its Ceftazidime that was the potential factor in backing the divergence of CTX-M. [50-51]

6. Plasmids and spread of bacterial genes: According to research studies the widespread dissemination of blaCTX-M gene is closely linked with IncF plasmid especially FII. IncF plasimds are epitome of autonomous replication and contributor to bacterial fitness and survival. These FII are narrow range plasmids whose significance is limited to horizontal gene transfer in closely related bacterial species like E.Coli, Salmonella and Shigella. These incF plasmids are usually in low number in the bacteria but harbor all

sorts of virulent gene.[52-53] These incompatibility plasmids are associated with gram negative bacteria and labelled 'epidemic resistant plasmid' because of their affinity to attain and transfer resistant elements among the bacteria. These plasmids have evolved through the recombination of various plasmids and thus are not homogenous. A notable fact about these plasmids is that these were prevalent among the *Enterobacteriaceae f*amily even before the use of antibiotic and were well adapted to these organisms.[54-55] These events without a doubt suggests the persistence and globalization of these resistant elements including blaCTX-M genes.[56-57]

Figure 2: Structure of *Enterbacteriacae* genetics elements (plasmids and transposons)



7. Dispersion of multi-drug resistant and virulent high-risk clones:

One of the reason allowing dissemination of enzyme elaborating CTX-M is the contribution of defined copies predominately from *K. pneumoniae* and *E. coli*. current research founded on MLST(Multi-Locus Sequence Typing) have confirmed although there is a varity amongst CTX-M producer, however few conjugated (clonal complexes) are commonly linked to CTX-M enzymes and designate high-risk clones st131 is example of international disseminated clone. At individual basis risk factors which allow adherence to the host and host adherence and binding also facilitate its perseverance and have been found in food products, wild-life, and animals.

8. *Salmonella typhi* **and CTM: the everlasting endemic**

Salomella typhi is held responsible for typhoid or enteric fever. Enteric fever is characterized by step-wise fever which if not treated immediately and properly, ends up in complication and mortality. This disease predominantly affects children below 10 years of age but recent reports suggest that it affects male in their 20's as well. This bacteria is transmitted to human by the consumptions of dirty water or contaminated food. Typhoid is common in developing countries mostly due improper sewerage system, larger families sharing single washroom, improper hygiene and mostly importantly unjust use of antibiotics. In the areas where *S.Typhi* is endemic different types of strains are circulating but only restricted strains cause outbreaks. In the year 1948 Chloramphenicol was introduced as the most efficient drug to treat typhoid fever. But in merely two years due to pervasive use of drugs, the first resistant isolate was reported. This battle became worrisome in the 1980s when resistant strains started emerging to the first line of antibiotics Co-trimoxazole, Chloramphenicol and Ampicillin, and these strain were defined as multidrug resistance (MDR).[58] Since then 3rd Cephalosporins have been used as empirical treatment of typhoid. In 1999, Bangladesh reported 1st XDR (extensively drug resistant) isolate. This isolate was resistant to ceftriaxone (3rd generation cephalosporin) as well as 1st like of drugs. In the following years various reports of 2-5 cases of XDR *S.Typhi* were being reported, raising concerns. In 2016 Pakistan reported a major "XDR endemic" in the city of Sindh effecting more than 500 in a week. According to Pakistan National Institute of Health, till the month of Aug 2021, in Karachi alone 1,739 XDR S.Typhi have been reported. Alongside "The Centers for Disease Control and Prevention" (CDC) declares that the world has once again entered the "post-antibiotic era," wherein we would face lack of effective treatment options due to marked antibiotic resistance (AMR).

The gene sequencing of these XDR *Salmonella* strains indicated that these belonged to haplotype 58 (H58) which elaborates CTX-M enzymes. S.Typhi has a remarkable capability to express CTX-M family that encompasses more than 200 enzymes. These enzymes degrade Ceftriaxone, Cefotaxime but CTX-M 15 enzymes also degrades Ceftazidime, leaving behind Carbapenems for the treatment, to which resistance has also started to emerge. The last decade shows substantial increase in CTX-M producing variants and most of the research has been conducted in the developed world. Studies in various countries show that once a β-lactamases enters a defined geographic area, it superimposes and replaces other ESBL variants. In this review our objective was to research the antibiotic resistant pattern in salmonella in our part of the world and look for the presence of CTX-M 15 gene of beta lactamases. Although other non-typhoidal Salmonella enterica serovar Typhimurium consist CTX-M-2, CTX-M55 and CTX-M27, Salmonella enterica serovar typhi affecting humans elaborates CTX-M14 and CTX-M15. It has been proposed that these typhiodal serovar caught CTX-M15 on their mobile genetic material e.g plasmid from *E.Coli* in sewerage water.

XDR *S.Typhi* were only reported from Pakistan, Bangladesh, India, Nepal and African countries.But recent reports from developed countries like England, Canada, USA etc has raised concerns of the authorities. The WGS of these strains indicated that they identical to the one's that caused endemic in Pakistan and India. The global reports of *S.Typhi*

elaborating CTX-M15 is alarming and tragic. Even before the advent of these strains, typhoid had killed and has affected millions of people. Typhoid has become a symbol of fear amongst many civilizations and if prompt measures are not taken to combat this strain, treating *S.Typhi* infection would become impossible.

CONCLUSION:

Although the magnitude of infections caused by antibiotic resistant *Enterobacteriaceae* strains vary globally but South East Asia remains a major reservoir of these resistant strains. The widespread and prominent amongst these are *E.coli*, *K.pneumoniae* and *S.Typhi*. Since last few years these strains have acquired further resistant elements, challenging the health care system to provide with the better treatment options. At this point of time it is of utmost importance to address these increasing XDR strains outbreaks especially from Pakistan, India and Bangladesh. The pooled prevalence of ESBL and MBL-producing E. coli in South Asia is 33% and 17% respectively. The prevalence of blaCTX-M type was 58% with blaCTX-M-15 being the most prevalent (51 %) variants.

Today CTX-M-type enzymes are the most commonly found ESBL type with the CTX-M-15 variant dominating worldwide, followed in prevalence by CTX-M-14, and CTX-M-27 is emerging in certain parts of the world. This ESBL *Enterobacteriaceae* (ESBL.E) can disseminate by direct contact with an infected person's bodily fluids (blood, urine, drainage from a wound, fecal matter). They may also spread by contact with surfaces or equipment harboring these bacteria's. Immigrations and travel from endemics areas is another prominent reason for increased dissemination. Thus this overhauled emergence of CTX-M gene is responsible for increasing reports of nosocomial infections, ICU outbreaks and related mortality. The CTX-M family warrants research and is a pattern reflecting increasing antibiotic resistance. Genetic sequences and data bases suggests that blaCTX-M have originated from *Kluyvera* spp and merging of these various genetic elements in various *Enterbacteriacaea* by mode of plasmids and clone. The co-existence of blaCTX-M genes with other resistant elements contributes towards the significant increase of CTX-m enzymes justifies the in-depth study so as to foresee a pandemic scenario of antibiotic resistance. Considering this we propose that rapid preventive measure should be implemented to control the widespread dissemination of these virulent strains. This constant evolution of ESBL.E should be controlled by monitoring the ESBL fecal carriage especially in ICU patients, assurance of hygiene protocols, screening of meat and dairy products, regular antibiograms indicating antibiotic susceptibility patterns in a given region, antimicrobial stewardship programs insuring synchronized and appropriate use of antibiotics, and restricted and monitored travel from endemic areas, and finally prohibiting injudicious use of antibiotics. The present and future from today is very critical because if we failed to control and restrict these antibiotic resistant strainss in Enterobacteriacaea we would unquestionably end up being in post antibiotic era, where only death and fever prevailed.

Authors Contribution:
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REFERENCE:

1. Davies J, Davies D. Origins and evolution of antibiotic resistance. Microbiology and molecular biology reviews. 2010 ;74(3):417-33. DOI:https://doi.org/ 10.1128 /MMBR. 00016-10
2. Tooke CL, Hinchliffe P, Bragginton EC, Colenso CK, Hirvonen VH, Takebayashi Y, Spencer J. β-Lactamases and β-Lactamase Inhibitors in the 21st Century. Journal of molecular biology. 2019;431(18):3472-500. https://doi.org/10.1016/ j.jmb. 2019. 04.002
3. Gonzaìlez-Bello C, Rodríguez D, Pernas M, Rodríguez Á, Colchoìn E. β-Lactamase inhibitors to restore the efficacy of antibiotics against superbugs. Journal of medicinal chemistry. 2019 ;63(5):1859-81. https://doi.org/10.1021/acs. jmedchem. 9b01279
4. Nagarjuna D, Mittal G, Dhanda RS, Gaind R, Yadav M. Alarming levels of antimicrobial resistance among sepsis patients admitted to ICU in a tertiary care hospital in India-a case control retrospective study. Antimicrobial Resistance & Infection Control. 2018;7(1):1-1. DOI:10.1186/s13756-018-0444-8
5. De Angelis G, Del Giacomo P, Posteraro B, Sanguinetti M, Tumbarello M. Molecular mechanisms, epidemiology, and clinical importance of β-lactam resistance in enterobacteriaceae. International Journal of Molecular Sciences. 2020; 21 (14): 5090. https://doi.org/10.3390/ijms21145090
6. Ramadan AA, Abdelaziz NA, Amin MA, Aziz RK. Novel bla CTX-M variants and genotype-phenotype correlations among clinical isolates of extended spectrum beta lactamase-producing Escherichia coli. Scientific reports. 2019 ;9(1):1-2 doi: 10.1038/ s41598-019-39730-0
7. Ainoda Y, Aoki K, Ishii Y, Okuda K, Furukawa H, Manabe R, Sahara T, Nakamura-Uchiyama F, Kurosu H, Ando Y, Fujisawa M. Klebsiella pneumoniae carbapenemase (KPC)-producing Klebsiella pneumoniae ST258 isolated from a Japanese patient without a history of foreign travel-a new public health concern in Japan: a case report. BMC infectious diseases. 2019;19(1):1- doi: 10.1186/s12879-018-3649-9.
8. Bhattacharya M, Toth M, Antunes NT, Smith CA, Vakulenko SB. Structure of the extended-spectrum class C β-lactamase ADC-1 from Acinetobacter baumannii. Acta Crystallographica Section D: Biological Crystallography. 2014 Mar 1;70(3):760-71 https://doi.org/10.1107/S1399004713033014
9. Gomi, R.; Matsuda, T.; Matsumura, Y.; Yamamoto, M.; Tanaka, M.; Ichiyama, S.; Yoneda, M.Occurrence of Clinically Important Lineages, Including the Sequence Type 131 C1-M27 Subclone, among Extended-Spectrum-bLactamase-Producing Escherichia coli in Wastewater. Antimicrob. Agents Chemother. 2017, 61, e00564-17. DOI:https://doi.org/10.1128 /AAC.00564-17

10. Castanheira M, Simner PJ, Bradford PA. Extended-spectrum β-lactamases: An update on their characteristics, epidemiology and detection. JAC-antimicrobial resistance. 2021 ;3(3): dlab092. https://doi.org/10.1093/jacamr/dlab092

11. Negeri AA, Mamo H, Gurung JM, Firoj Mahmud AK, Fällman M, Seyoum ET, Feleke Desta A, Francis MS. Antimicrobial Resistance Profiling and Molecular Epidemiological Analysis of Extended Spectrum β-Lactamases Produced by Extraintestinal Invasive Escherichia coli Isolates From Ethiopia: The Presence of International High-Risk Clones ST131 and ST410 Revealed. Frontiers in Microbiology. 2021:2159. https://doi.org/10.3389/fmicb.2021.706846

12. Bevan ER, Jones AM, Hawkey PM. Global epidemiology of CTX-M β-lactamases: temporal and geographical shifts in genotype. Journal of antimicrobial chemotherapy. 2017 Aug 1;72(8):2145 55. https://doi.org/10.1093/jac/dkx146

13. Mlynarcik P, Chudobova H, Zdarska V, Kolar M. In Silico Analysis of Extended-Spectrum β-Lactamases in Bacteria. Antibiotics. 2021;10(7):812. https://doi.org/10.3390 /antibiotics 10070812

15. Mathers AJ, Peirano G, Pitout JD. The role of epidemic resistance plasmids and international high-risk clones in the spread of multidrug-resistant Enterobacteriaceae. Clinical microbiology reviews. 2015 Jul;28(3):565-91. DOI:https://doi.org/10.1128/CMR.00116-14 •

16. Bush K, Bradford PA. Epidemiology of β-lactamase-producing pathogens. Clinical microbiology reviews. 2020;33 (2): e00047 -19. DOI:https://doi.org/10.1128/CMR.00047-19

17. Bauernfeind A, Stemplinger I, Jungwirth R, Ernst S, Casellas JM. Sequences of beta-lactamase genes encoding CTX-M-1 (MEN-1) and CTX-M-2 and relationship of their amino acid sequences with those of other beta-lactamases. Antimicrobial agents and chemotherapy. 1996;40(2):509-13. DOI:https://doi.org/10.1128/AAC.40.2.509

18. Matinfar S, Ahmadi M, Sisakht AM, Sadeghi J, Javedansirat S. Phylogenetic and antibiotics resistance in extended-spectrum B-lactamase (ESBL) Uropathogenic Escherichia coli: An update review. Gene Reports. 2021:101168. https://doi.org/ 10.1016 /j.genrep.2021.101168

19. Zainab SM, Junaid M, Xu N, Malik RN. Antibiotics and antibiotic resistant genes (ARGs) in groundwater: A global review on dissemination, sources, interactions, environmental and human health risks. Water research. 2020:116455. https:// doi.org/10.1016/j.watres.2020.116455Get

20. Van den Bunt G, van Pelt W, Hidalgo L, Scharringa J, de Greeff SC, Schürch AC, Mughini-Gras L, Bonten MJ, Fluit AC. Prevalence, risk factors and genetic characterisation of extended-spectrum beta-lactamase and carbapenemase-producing Enterobacteriaceae (ESBL-E and CPE): a community-based cross-sectional study, the Netherlands, 2014 to 2016. Eurosurveillance. 2019;24(41):1800594 https://doi.org /10.2807/1560-7917.ES.2019.24.41.1800594

21. Palmeira JD, Ferreira HM. Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae in cattle production–a threat around the world. Heliyon. 2020;6(1):e03206. https://doi.org/10.1016/j.heliyon.2020.e03206

22. Jian Z, Zeng L, Xu T, Sun S, Yan S, Yang L, Huang Y, Jia J, Dou T. Antibiotic resistance genes in bacteria: Occurrence, spread, and control. Journal of Basic Microbiology. 2021 https://doi.org/10.1002/jobm.202100201

23. Rasoulinasab M, Shahcheraghi F, Feizabadi MM, Nikmanesh B, Hajihasani A, Aslani MM. Distribution of ciprofloxacin-resistance genes among ST131 and non-ST131 clones of Escherichia coli isolates with ESBL phenotypes isolated from women with urinary tract infection. Iranian Journal of Microbiology. 2021;13(3):294. doi: 10.18502/ijm.v13i3.6389

24. Musila L, Kyany'a C, Maybank R, Stam J, Oundo V, Sang W. Detection of diverse carbapenem and multidrug resistance genes and high-risk strain types among carbapenem non-susceptible clinical isolates of target gram-negative bacteria in Kenya. Plos one. 2021;16(2):e0246937. https://doi.org/ 10. 1371 /journal.pone.0246937

25. Azargun R, Gholizadeh P, Sadeghi V, Hosainzadegan H, Tarhriz V, Memar MY, Pormohammad A, Eyvazi S. Molecular mechanisms associated with quinolone resistance in Enterobacteriaceae: review and update. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2020; 114(10):770-81. https://doi.org/10.1093/trstmh/traa041

26. Latifi B, Tajbakhsh S, Ahadi L, Yousefi F. Coexistence of aminoglycoside resistance genes in CTX-M-producing isolates of Klebsiella pneumoniae in Bushehr province, Iran. Iranian Journal of Microbiology. 2021;13(2):161 doi: 10.18502/ ijm.v13i2.5975

27. Phoba MF, Barbé B, Lunguya O, Masendu L, Lulengwa D, Dougan G, Wong VK, Bertrand S, Ceyssens PJ, Jacobs J, Van Puyvelde S. Salmonella enterica serovar Typhi producing CTX-M-15 extended spectrum β-lactamase in the Democratic Republic of the Congo. Clinical Infectious Diseases. 2017 ; 65(7):1229-31. https://doi.org/10.1093/cid/cix342

28. Girlich D, Bonnin RA, Naas T. Occurrence and diversity of CTX-M-producing Escherichia coli from the Seine river. Frontiers in Microbiology. 2020;11. https://doi.org/10.3389 /fmicb.2020.603578

29. Osiñska M, Nowakiewicz A, Ziêba P, Gnat S, £agowski D. A rich mosaic of resistance in extended-spectrum β-lactamase-producing Escherichia coli isolated from red foxes (Vulpes vulpes) in Poland as a potential effect of increasing synanthropization. Science of The Total Environment. 2021 :151834. https://doi.org/10.1016/ j.scitotenv. 2021. 151834

30. Bauernfeind A, Schweighart S, Grimm H. A new plasmidic cefotaximase in a clinical isolate of Escherichia coli. Infection. 1990 Sep 1;18(5):294-8.

31. Oliver A, Pérez-Dýìaz JC, Coque TM, Baquero F, Cantón R. Nucleotide sequence and characterization of a novel cefotaxime-hydrolyzing β-lactamase (CTX-M-10) isolated in Spain. Antimicrobial agents and chemotherapy. 2001;45(2):616-20. DOI: https://doi.org/10.1128 /AAC. 45. 2. 616-620.2001

32. Karim A, Poirel L, Nagarajan S, Nordmann P. Plasmid-mediated extended-spectrum β-lactamase (CTX-M-3 like) from India and gene association with insertion sequence IS Ecp1. FEMS microbiology letters. 2001;201(2):237-41. https://doi.org/10.1111/j.1574-6968.2001.tb10762.x

33. Abd El Baqy FA, Rizk MS, Haggag YN, Nossair MA, Mansour AM, Elaadli H. Prevalence of Some Extended Spectrum β-Lactamase Producing Enterobacteriaceae in Human: A Retrospective Study. Alexandria Journal for Veterinary Sciences. 2021;69(1). https://doi.org/10.1111/j.1574-6968. 2001.tb10762.x

34. Jabalameli L, Beigverdi R, Ranjbar HH, Pouriran R, Jabalameli F, Emaneini M. Phenotypic and Genotypic Prevalence of Extended-Spectrum β-Lactamase-Producing Escherichia coli: A Systematic Review and Meta-Analysis in Iran. Microbial Drug Resistance. 2021;27(1):73-86. https://doi.org/10. 1089/ mdr.2019.0396

35. Coque TM, Novais Â, Carattoli A, Poirel L, Pitout J, Peixe L, Baquero F, Cantón R, Nordmann P. Dissemination of clonally related Escherichia coli strains expressing extended-spectrum β-lactamase CTX-M-15. Emerging infectious diseases. 2008;14(2):195. doi: 10.3201/eid1402.070350

36. Pérez-Moreno, M.O., Moral-Parras, P., Domenech-Spanedda, M.F., Casacuberta-Barberà, N., Bas-García, I., Centelles-Serrano, M.J. and Vila-Pérez, M., 2021. Extended-Spectrum β-Lactamase-and Carbapenemase-Producing Enterobacterales Intestinal Carriage Among Outpatients: Microbiological and Epidemiological Differences Between Private Dwelling Residents and Nursing Home Residents. Microbial Drug Resistance, 27(7), pp.879-888. https://doi.org/ 10.1089/ mdr. 2020.0201

37. Subramanya SH, Bairy I, Metok Y, Baral BP, Gautam D, Nayak N. Detection and characterization of ESBL-producing Enterobacteriaceae from the gut of subsistence farmers, their livestock, and the surrounding environment in rural Nepal. Scientific reports. 2021;11(1):1-3.DOI 10.1038/s41598-021-81315-3

38. Martínez MM, Bonomo RA, Vila AJ, Maffía PC, González LJ. On the Offensive: the Role of Outer Membrane Vesicles in the Successful Dissemination of New Delhi Metallo-β-lactamase (NDM-1). Mbio. 2021;12(5):e01836-21. DOI: https://doi.org/10.1128/mBio.01836-21

39. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, Chaudhary U, Doumith M, Giske CG, Irfan S, Krishnan P. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. The Lancet infectious diseases. 2010 ;10(9):597-602. https://doi.org/10.1016/S1473-3099(10)70143-2

40. Sia CM, Baines SL, Valcanis M, Lee DY, da Silva AG, Ballard SA, Easton M, Seemann T, Howden BP, Ingle DJ, Williamson DA. Genomic diversity of antimicrobial resistance in non-typhoidal Salmonella in Victoria, Australia. Microbial Genomics. 2021 ;7(12):000725. doi: 10.1099/mgen.0.000725

41. Ejaz H, Younas S, Abosalif KO, Junaid K, Alzahrani B, Alsrhani A, Abdalla AE, Ullah MI, Qamar MU, Hamam SS. Molecular analysis of bla SHV, bla TEM, and bla CTX-M in extended-spectrum β-lactamase producing Enterobacteriaceae recovered from fecal specimens of animals. Plos one. 2021; 16(1):e0245126. https://doi.org/10.1371 /journal. pone.0245126

42. Matsumoto Y, Kitazume H, Yamada M, Ishiguro Y, Muto T, Izumiya H, Watanabe H. CTX-M-14 type beta-lactamase producing Salmonella enterica serovar Enteritidis isolated from imported chicken meat. Japanese journal of infectious diseases. 2007;60(4):236.

43. Kiros T, Workineh L, Tiruneh T, Eyayu T, Damtie S, Belete D. Prevalence of Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae in Ethiopia: A Systematic Review and Meta-Analysis. International journal of microbiology. 2021; 2021. https://doi.org/10.1155/2021/6669778

44. Souna D, Drissi M, Almahmoud I, Maurin M. Enterobacter cloacae Complex and CTX-M Extended-Spectrum β-Lactamases in Algeria. Microbial Drug Resistance. 2021. http://doi.org/10.1089/mdr.2020.0535

45. Jacobs MR, Abdelhamed AM, Good CE, Rhoads DD, Hujer KM, Hujer AM, Domitrovic TN, Rudin SD, Richter SS, van Duin D, Kreiswirth BN. ARGONAUT-I: activity of cefiderocol (S-649266), a siderophore cephalosporin, against Gram-negative bacteria, including carbapenem-resistant nonfermenters and Enterobacteriaceae with defined extended-spectrum β-lactamases and carbapenemases. Antimicrobial agents and chemotherapy. 2019;63(1):e01801-18. DOI:https:/ /doi.org /10.1128/AAC.01801-18

46. Vinothkumar K, Bhalara SR, Shah A, Ramamurthy T, Niyogi SK, Kumar GN, Bhardwaj AK. Involvement of topoisomerase mutations and qnr and aac (6') Ib-cr genes in conferring quinolone resistance to clinical isolates of Vibrio and Shigella spp. from Kolkata, India (1998–2009). Journal of Global Antimicrobial Resistance. 2018;13:85-90. https://doi.org/ 10.1016 /j.jgar.2017.10.013

47. Azargun R, Sadeghi MR, Barhaghi MH, Kafil HS, Yeganeh F, Oskouee MA, Ghotaslou R. The prevalence of plasmid-mediated quinolone resistance and ESBL-production in Enterobacteriaceae isolated from urinary tract infections. Infection and drug resistance. 2018;11:1007. doi: 10.2147/ IDR.S160720

48. Farmer 3rd JJ, Fanning GR, Huntley-Carter GP, Holmes B, Hickman FW, Richard C, Brenner DJ. Kluyvera, a new (redefined) genus in the family Enterobacteriaceae: identification of Kluyvera ascorbata sp. nov. and Kluyvera cryocrescens sp. nov. in clinical specimens. Journal of Clinical Microbiology. 1981;13(5):919-33. DOI:https://doi.org/ 10.1128/jcm.13.5.919-933.1981

49. Bevan ER, Jones AM, Hawkey PM. Global epidemiology of CTX-M β-lactamases: temporal and geographical shifts in genotype. Journal of antimicrobial chemotherapy. 2017;72(8):2145-55. https://doi.org/10.1093/jac/dkx146

50. Palzkill T. Structural and mechanistic basis for extended-spectrum drug-resistance mutations in altering the specificity of TEM, CTX-M, and KPC β-lactamases. Frontiers in molecular biosciences. 2018;5:16. https://doi.org/ 10.3389/ fmolb.2018.00016

51. Hussain HI, Aqib AI, Seleem MN, Shabbir MA, Hao H, Iqbal Z, Kulyar MF, Zaheer T, Li K. Genetic basis of molecular mechanisms in β-lactam resistant gram-negative bacteria. Microbial Pathogenesis. 2021:105040. https://doi.org/ 10.1016/ j.micpath.2021.105040

52. Carattoli A. Resistance plasmid families in Enterobacteriaceae. Antimicrobial agents and chemotherapy. 2009;53(6):2227-38. DOI:https://doi.org/10.1128/AAC.01707-08

53. Datta N, Dacey S, Hughes V, Knight S, Richards H, Williams G, Casewell M, Shannon KP. Distribution of genes for trimethoprim and gentamicin resistance in bacteria and their plasmids in a general hospital. Microbiology. 1980;118(2):495-508. https://doi.org/10.1099/00221287-118-2-495

54. Carattoli A, Villa L, Fortini D, García-Fernández A. Contemporary IncI1 plasmids involved in the transmission and spread of antimicrobial resistance in Enterobacteriaceae. Plasmid. 2021;118:102392. https://doi.org/10.1016 /j.plasmid .2018.12.001

55. Dong H, Li Y, Cheng J, Xia Z, Liu W, Yan T, Chen F, Wang Z, Li R, Shi J, Qin S. Genomic Epidemiology Insights on NDM-Producing Pathogens Revealed the Pivotal Role of Plasmids on bla NDM Transmission. Microbiology Spectrum. 2022:e02156-21. DOI:https://doi.org/ 10.1128/spectrum. 02156-21

56. Villegas MV, Jiménez A, Esparza G, Appel TM. Carbapenemase-producing Enterobacteriaceae: A diagnostic, epidemiological and therapeutic challenge. Infectio. 2019 Dec;23(4):358-68. https://doi.org/10.22354/in.v23i4.808

57. Mirza S, Kariuki S, Mamun KZ, Beeching NJ, Hart CA. Analysis of plasmid and chromosomal DNA of multidrug-resistant Salmonella enterica serovar Typhi from Asia. Journal of Clinical Microbiology. 2000;38(4):1449-52. DOI:https://doi.org/10.1128/JCM.38.4.1449-1452.2000

58. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019. US Department of Health and Human Services, Centres for Disease Control and Prevention; 2019.

59. Poirel L, de la Rosa JM, Richard A, Aires-de-Sousa M, Nordmann P. CTX-M-33 is a CTX-M-15 derivative conferring reduced susceptibility to carbapenems. Antimicrobial agents and chemotherapy. 2019;63(12):e01515-19. doi: 10.1128/AAC. 01515-19 PMCID: PMC6879240

60. Seki LM, Pereira PS, de Souza Conceição M, Souza MJ, Marques EA, Carballido JM, de Carvalho ME, Assef AP, Asensi MD. Molecular epidemiology of CTX-M producing Enterobacteriaceae isolated from bloodstream infections in Rio de Janeiro, Brazil: emergence of CTX-M-15. The Brazilian Journal of Infectious Diseases. 2013;17(6):640-6.

61. Schmiedel J, Falgenhauer L, Domann E, Bauerfeind R, Prenger-Berninghoff E, Imirzalioglu C, Chakraborty T. Multiresistant extended-spectrum β-lactamase-producing Enterobacteriaceae from humans, companion animals and horses in central Hesse, Germany. BMC microbiology. 2014;14(1):1-3.

62. Lartigue MF, Zinsius C, Wenger A, Bille J, Poirel L, Nordmann P. Extended-spectrum β-lactamases of the CTX-M type now in Switzerland. Antimicrobial agents and chemotherapy. 2007 ;51(8) :2855-60.

Case Report **Open Access**

Aesthetic Anxiety in a Child with Cleidocranial Dysplasia

Ayesha Shahid, Arooj Aman, Amna Malik

ABSTRACT

Cleidocranial dysplasia (CCD) is a rare syndrome that affects the skeleton and teeth. It is characterized by absent or hypoplastic clavicles, mobile shoulder girdles, patent fontanelles, supernumerary teeth, retained deciduous and delayed permanent teeth. A 10 year old boy with CCD is reported with chief complaints of aesthetics and dental pain. The bullying and social agony at a tender age were alarming as the patient was highly distressed regarding his missing teeth. Juvenile aesthetic concerns and the psychosocial impact were emphasized in this case. He was treated with manual scaling, pulp therapy, restoration, and a prosthesis to speedily replace his missing teeth. Long-term orthodontic treatment was suggested. Due to the early diagnosis, a better prognosis exists for multidisciplinary treatment. Counselling was pivotal for dealing with his aesthetic anxiety and oral health. Special attention should be given to the aesthetics and psychosocial state of patients with syndromes in underdeveloped societies.

Keywords: Aesthetic anxiety, cleidocranial dysplasia syndrome, dental treatment, psychosocial stigma, young male

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INTRODUCTION:

Cleidocranial dysplasia (CCD) is a "one in millions" rare congenital disorder commonly caused by RUNX2 gene mutation, in which endochondral and intramembranous bone formation is defective. RUNX2 is involved in the osteoblastic lineage of stem cells.[1] Calvaria and clavicles are primarily affected in this autosomal dominant disorder, with absent clavicles in 10% of the cases.[2] Common findings are aplastic or hypoplastic clavicles, Wormian bones, incompletely closed fontanelles, short stature, retained deciduous dentition, delayed eruption of permanent teeth, supernumerary teeth, brachycephaly, hypertelorism, frontal bossing, etcetera.[3] Other skeletal anomalies may include small and bell-shaped thoracic cage, mobile shoulder girdle, underdeveloped maxilla, malformed paranasal sinuses, and bone defects. CCD patients are easily diagnosed by abnormalities of clavicles, skull, and dentition.[4]

The deranged skeletal features in CCD may cause aesthetic anxiety in patients which may hinder their social integration. Missing anterior teeth affects social life and may lead to other clinical issues.[5] The orodental anomalies are of utmost clinical significance to dentists, who should be able to diagnose the syndrome. Multidisciplinary management is required to restore aesthetics and function. A case of CCD is presented in this report with aesthetic distress at a young age.

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CASE

A 10 year old boy of Pashtun origin presented to the Islamic International Dental Hospital, Islamabad in March 2019, with complaints of both aesthetic distress and dental pain. He complained that children in his madrassa bully him about his lack of anterior teeth, which traumatized him. On examination, he had visibly deficient clavicles and abnormal mobility of the shoulders. He was able to bring the humeral heads close to each other (Figure-1). He had short stature and a very lean body for his age. He had a long and narrow face (dolichofacial) with anterior divergence, mid-face deficiency, frontal bossing, hypertelorism, depressed nasal bridge, and depressed zygomatic bones. He was diagnosed with CCD and had no family history. His father gave consent on behalf of the child to be photographed and published. Chest x-ray posteroanterior view showed the absence of a right clavicle and a hypoplastic left clavicle, bell-shaped thorax, and low-placed scapulas (Figure-2). Upon intraoral examination, a narrow, "V" shaped, and high vault palate was seen. The patient had several impacted permanent teeth, malocclusion class 3, and #46 was in posterior buccal crossbite. Among permanent teeth, the upper arch had 14, 16 and 26 erupted whereas the orthopantomograph showed impacted 11, 12, 13, 15, 21, 22, 23, 24, and 25 (Figure-3). Broken down roots (BDRs) of deciduous 55, 64 and 65 were

present whereas 53, 62 and 63 were retained. The lower arch had entire deciduous teeth retained and only 36 and 46 erupted. There was pain on percussion in #46 and the periapical x-ray showed deep caries. No supernumerary teeth were present. Lateral cephalogram showed a hypoplastic maxilla, long y-axis and large FMA, indicating class 3 mandibular prognathism, and a high vertical growth pattern (Figure-3). An anteroposterior view of the skull showed normal sutures (Figure-3) Dental scaling was manually performed and residual roots were extracted. It was followed by pulpectomy of the carious tooth with a Glass ionomer cement (GIC) restoration. Upper and lower anterior partial dentures were made for aesthetic purposes, with spaces underneath for the permanent teeth to erupt. The patient was called for follow-up visits where the acrylic of the denture was trimmed whenever the teeth erupted further (Figure-4). For the skeletal class 3 mandibular prognathism, occlusal chin cups were presently advised. Orthodontic treatment for the eruption of teeth was also suggested which the patient refused. The patient was counseled for his aesthetic anxieties and oral hygiene maintenance. He was referred to orthopedics for stabilization of his shoulders. The patient was extremely satisfied with the prosthesis.

Figure 1: Frontal profile of patient showing hypermobile shoulders and deficient clavicles

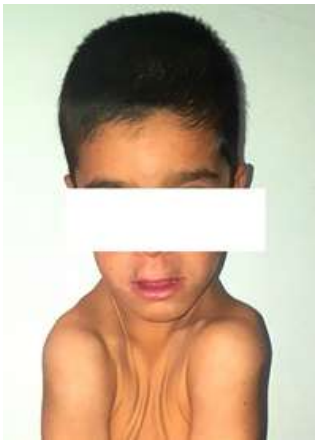
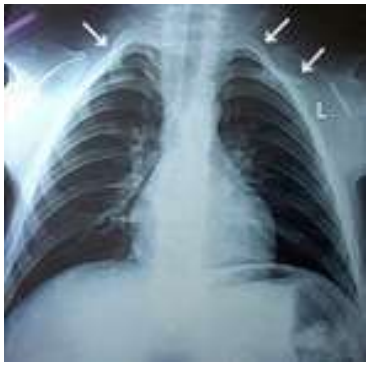


Figure 2: Chest radiograph posteroanterior view showing bell-shaped thorax. The arrow on the right side shows the absence of a clavicle and the arrows on the left side show a hyperplastic clavicle



DISCUSSION

A child's environment plays a key role in the development of sound social and mental health. McNamara et al. reported that 93.5% of CCD patients present with dental abnormalities.[6] Since the case had visible anomalies, he was subjected to traumatic bullying and psychosocial anxiety even at the tender age of ten. Similarly, Garg and Agrawal reported an adult male CCD patient who was also psychologically traumatized due to missing teeth and societal abandonment. He also reported speech and communication barriers and wanted rapid dental restoration.[4] Alves and Oliveira also reported an adult female CCD patient with aesthetic agony and the need for speedy restoration of teeth.[7] This implies the aesthetic vulnerability of CCD patients, not only in mature adults but juvenile patients as well. Similar to this case, Tristão et al. concluded in their systematic review that dental malocclusion is related to increased bullying in children and teenagers.[8] Aesthetic concerns in children due to syndromes like cleft lip and palate have also

Figure 3: Radiographs of the patient. (a) Anteroposterior view of skull. (b) Lateral cephalogram. (c) Orthopantomograph showing several impacted permanent teeth and few retained deciduous teeth

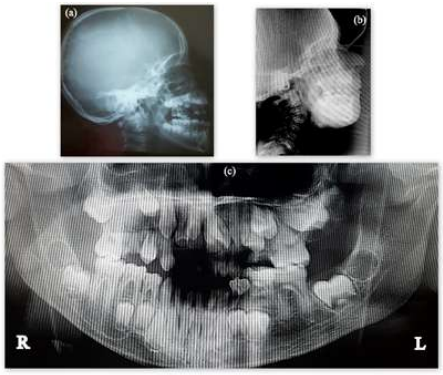
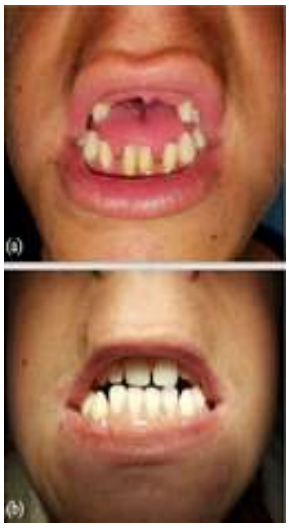


Figure 4: (a) Pre-treatment facial profile. (b) Post-treatment aesthetic facial profile with prostheses



(a)

(b)

been reported, where the children report psychosocial agony.[9] Surprisingly, some other case reports of pediatric CCD did not evaluate the aesthetics related anxiety, the social or mental health of the children.[10,11] This is alarmingly important in underdeveloped countries where the aesthetic anxieties of children and their mental health and self-esteem are not emphasized. Psychological assessment and counselling of patients with congenital deformities must always be performed.

The treatment planning for CCD should be focused on a functional and aesthetic outcome.[12] Treatment usually consists of extraction of retained deciduous and supernumerary teeth at an accurate time to guide the eruption of permanent teeth with the help of orthodontic traction and elastics. Orthodontics and oral surgery combine the goal of correction of mandibular prognathism.[13] The rapid and non-invasive treatment modality includes tooth-supported prosthesis.[14] This case has been reported due to the rarity of CCD and its associated aesthetic trauma in a child.

CONCLUSION

A multidisciplinary approach is required for the rehabilitation of function and aesthetics of CCD patients. Even in pediatric patients, aesthetic concerns should be treated earnestly. Counselling the patients about their aesthetic anxieties and healthcare is pivotal for their self-esteem and social life.

Authors Contribution:
Ayesha Shahid: Research conception, case management, design, writing the final draft, data collection and analysis
Arooj Aman: Research conception, design, writing initial draft and data collection and analysis.
Amna Malik: Research design, editing the draft data, data collection and analysis.

REFERENCES

1. Motaei J, Salmaninejad A, Jamali E, Khorsand I, Ahmadvand M, Shabani S, et al. Molecular genetics of cleidocranial dysplasia. Fetal Pediatr Pathol. 2021;6;40(5):442-54. DOI: https://doi.org/10.1080/15513815.2019.1710792
2. Pan CY, Tseng YC, Lan TH, Chang HP. Craniofacial features of cleidocranial dysplasia. J Dent Sci. 2017;1;12(4):313-8. DOI: https://doi.org/10.1016/j.jds.2017.07.002
3. Mundlos S, Otto F, Mundlos C, Mulliken JB, Aylsworth AS, Albright S, et al. Mutations involving the transcription factor CBFA1 cause cleidocranial dysplasia. Cell. 1997;30;89(5):773-9. DOI: https://doi.org/10.1016/S0092-8674(00)80260-3
4. Garg RK, Agrawal P. Clinical spectrum of cleidocranial dysplasia: a case report. Cases J. 2008;1(1):1-4. DOI: https://doi.org/10.1186/1757-1626-1-377
5. Hemalatha R, Balasubramaniam MR. Cleidocranial dysplasia: A case report. J Indian Soc Pedod Prev Dent. 2008;1;26(1):40. DOI:10.4103/0970-4388.40322
6. McNamara CM, O'Riordan BC, Blake M, Sandy JR. Cleidocranial dysplasia: radiological appearances on dental panoramic radiography. Dentomaxillofac Radiol. 1999; 28(2):89-97. DOI: http://dx.doi.org/10.1038/sj /dmfr /4600417
7. Alves N, Oliveira RD. Cleidocranial dysplasia: a case report. Int J Morphol. 2008;26(4):1065-8. DOI: http://dx.doi.org/10.4067/S0717-95022008000400043
8. Tristão SK, Magno MB, Pintor AV, Christovam IF, Ferreira DM, Maia LC, de Souza IP. Is there a relationship between malocclusion and bullying? A systematic review. Prog Orthod. 2020;21(1):1-3. DOI: https://doi.org/10.1186/s40510-020-00323-7
9. Glener AD, Allori AC, Shammas RL, Carlson AR, Pien IJ, Aylsworth AS, et al. A population-based exploration of the social implications associated with cleft lip and/or palate. Plast Reconstr Surg. 2017;5(6):e1373. DOI: 10.1097/GOX.0000000000001373
10. Shen Z, Chun C, Wang R, Yan Z. Cleidocranial Dysplasia: Report of 3 Cases and Literature Review. Clin Pediatr. 2009;48(2):194-198. DOI:10.1177/0009922808323107
11. Vishnurekha C, Kalaivanan D, Krishnamoorthy S, Manoharan S, Kalyanaraman V, Selvaraj S. Cleidocranial Dysplasia in a 10-year-old Child: A Case Report. Int J Clin Pediatr Dent. 2019;12(4):352-5. DOI: 10.5005/jp-journals-10005-1634
12. Sagisaka T, Tai K, Flores G, Park JH. Management of cleidocranial dysplasia. J World Fed Orthod. 2015;1;4(1):23-30. DOI: https://doi.org/10.1016/j.ejwf.2014.11.001
13. Rocha R, Zasso MB, Floriano G, Derech C, Ribeiro GU, Locks A, et al. Orthodontic traction in a patient with cleidocranial dysplasia: 3 years of follow-up. Am J Orthod Dentofacial Orthop. 2014;1;146(1):108-18. DOI: https://doi.org/ 10.1016/j.ajodo.2013.09.016
14. D'Alessandro G, Tagariello T, Piana G. Craniofacial changes and treatment of the stomatognathic system in subjects with Cleidocranial dysplasia. Eur J Paediatr Dent. 2010 Mar 1;11(1):39-43.

Letter to Editor **Open Access**

Dilemma of Dantrolene: A life-saving drug unavailable in Pakistan

Tahir Ali, Habib Feroz Kapadia

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Malignant hyperthermia (MH) is brought on by a number of anaesthetic drugs, primarily succinylcholine and inhalation anesthetics.[1] It is a hypermetabolic reaction in those who are genetically predisposed. The pathophysiology of MH is associated with rise in myoplasmic calcium, which in turn triggers metabolic reactions that ends in hypermetabolism. This includes a rise in heart rate, a rise in body temperature, additionally acidosis.[2] Dantrolene is the only specific treatment for MH crises currently available. It is a post-synaptic muscle relaxant that reduces the excitation-contraction coupling of muscle cells by inhibiting the release of Ca^{2+} ions from the sarcoplasmic reticulum. Literature cites that in absence of this drug, mortality may reach up to 80%.[3] Studies are reporting an incidence of MH ranging from 1:10,000 to 1:150,000. Anesthesiologists are familiar with these rare genetic disorders and most might have encountered one or two cases in there career.[4]

The Malignant Hyperthermia Association of the United States (MHAUS) has recommended that Dantrolene be injected into suspected patients within 10 minutes.[5] Dantrolene is regrettably unavailable in Pakistan. The main obstacles to the drug's accessibility are its high price, lack of local production, no directions from authorities to make its availability a necessary requirement and its short shelf life. Dantrolene vials have a two-year shelf life on average. An initial dose of Dantrolene sodium for an adult patient requires approximately 12 vials at a dosage of 20 mg each vial. Following that, another 24 vials would be needed.[6]

This unavailability of such an important life-saving drug in majority of the hospitals in Pakistan raises serious concerns for all health care providers specially anesthetists and more importantly this puts our patients at risk. Early recognition of signs in patients is critical for anesthetists to start supporting therapies immediately, so favorable outcome can be achieved for patients, but for most the treatment is limited to supportive as drugs required for treatment is absent.

Anesthesiologists are asked to report MH episodes, and there is an urgent need to establish a telephone hotline in the nation that is accessible to all citizens and a national MH website that is accessible from anywhere in the country. Since this complication is uncommon and has terrible effects, it is important to establish a repository where all instances may be reported and made readily accessible to the entire health care community as needed.

In conclusion, Pakistan where Dantrolene is not available; treatment of malignant hypothermia is a major challenge. Early warning and recognition with prompt and effective treatment are essential for patients.

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Habib Feroz Kapadia: Conception and lietrature search

REFERENCES:

1. Blais A. Succinylcholine, malignant hyperthermia and rhabdomyolysis. CMAJ. 2022;194(25):E878. DOI: https://doi.org/10.1503/cmaj.146480-l
2. Neto CN, Neville MF, da Silva HC. Anesthesia for malignant hyperthermia susceptible patients. InTreatments, Mechanisms, and Adverse Reactions of Anesthetics and Analgesics 2022 (pp. 3-14). Academic Press. https://doi.org/10.1016/B978-0-12-820237-1.00001-6
3. Dar IS, Ashraf M. Pathophysiology of malignant hyperthermia. Perioperative Anaesthetic Emergencies. 2021:272.
4. Bin X, Wang B, Tang Z. Malignant Hyperthermia: A Killer If Ignored. Journal of PeriAnesthesia Nursing. 2022 Apr 10. https://doi.org/10.1016/j.jopan.2021.08.018
5. Hopkins PM, Girard T, Dalay S, Jenkins B, Thacker A, Patteril M, McGrady E. Malignant hyperthermia 2020: Guideline from the Association of Anaesthetists. Anaesthesia. 2021; 76(5):655-64. https://doi.org/10.1111/anae.15317
6. Smith A. Donating Dantrolene: Development and Implementation of a Malignant Hyperthermia Program in a Scarce Resource Setting. AANA journal. 2022;90(4).

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