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Dengue Fever

Chief Editor, PMJN, NAMS, Bir Hospital

Dengue fever in Nepal, as in many parts of South Asia, is now an annual epidemic usually post-monsoon, presents a growing threat to Nepalese people. This trend for increased magnitude has since continued with the number of outbreaks reported each year in many districts- Chitwan, Jhapa, Parsa (2012-2013), Jhapa, Chitwan (2015-2016), Rupandehi, Jhapa, Mahottari (2017), Kaski (2018) and Sunsari (2019). This season in 2023 epidemic of dengue fever was more in eastern part of Nepal and mortality was high there.

Dengue is tropical flu and is the most rapidly spreading mosquito-borne disease caused by flavivirus. The disease has become a major health concern in tropical and many subtropical areas. An estimated 96 million clinical dengue infections occur worldwide annually. In the absence of specific treatment, vector control is only one measure of dengue control activities.

Dengue fever is a disease with a mortality rate of less than 1%. When treated, dengue hemorrhagic fever has a mortality rate of 2-5%. When left untreated, dengue hemorrhagic fever has a mortality rate as high as 50%. Survivors usually recover without sequelae and develop immunity to the infecting serotype. Dengue is vectored by female mosquitoes Aedes aegypti in urban areas and Aedes albopictus mostly in rural areas. Humans are infected by all four serotypes DENV1, DENV2, DENV3, and DENV4. Rainfall and humidity factors, lack of vector control measures and the absence of anti-dengue antiviral drugs to date, are responsible for now spreading the disease globally worldwide. All 4 dengue serotypes exist in Nepal, with DENV-1 historically contributing the highest burden. The first case of dengue was reported in 2004.

Early diagnosis of the disease can prevent fatal cases. The early diagnosis of dengue is based on the detection of the NS1 antigen, while the search for IgM antibodies can only be done after the 6th day after the onset of fever. Confirmation of the diagnosis can be direct by detection of viral genomic DNA or its SN1 antigen, or indirect by detection of specific antibodies (IgM and IgG) in the blood. This may permit to distinguish acute primary and acute secondary dengue infections. Early diagnosis can be obtained by gene amplification (RT-PCR) or by detection of NS1 antigen of the virus. Simultaneous detection of NS1protein and IgM antibodies markers is useful to diagnose acute dengue infection.

One of the complications of Dengue is shock due to severe plasma leakage, fluid accumulation causing respiratory distress and the presence of severe bleeding or severe organ dysfunction. It is observed that there is a change in Platelet count from mild to severe form, platelet dysfunction and liver dysfunction leading to various degrees of bleeding manifestation.
Recently, the traditional World Health Organization (WHO) dengue classification (classic DF, Dengue Hemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS) were replaced with Dengue without Warning Signs, Dengue with Warning Signs and Severe Dengue (SD).

Analgesic Effect of Ultrasound Guided Paravertebral Block in Laparoscopic Cholecystectomy

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ABSTRACT

INTRODUCTION: Laparoscopic cholecystectomy is the most commonly performed surgical procedure in an adult population. Though it's a minimally invasive procedure, significant proportion of patients have severe postoperative pain. Pain following laparoscopic cholecystectomy is multifactorial and complex in nature. Several modalities have been used to manage this pain. Ultrasound guided bilateral paravertebral block is one of the emerging technique. We aimed to evaluate the analgesic effect of ultrasound guided bilateral paravertebral block in patient undergoing laparoscopic cholecystectomy.

METHOD: This is a clinical prospective, observational study. Fifty two patients, aged 18-70 years, American society of anesthesiologist (ASA) classification I and II scheduled for elective laparoscopic cholecystectomy under general anesthesia were enrolled and divided in two groups. Group1, received general anesthesia and ultrasound guided bilateral paravertebral block with Ropivacaine 20 ml 0.25% in each side group2 received general anesthesia without any block. We observed intraoperative additional fentanyl requirement and time of first rescue analgesia.

RESULT: In group1, none of the patient required additional intraoperative analgesia where as in group 2, 15.38 % (4/26) required additional analgesic, (p=0.045).Time of first rescue analgesia was longer (161.26 ±138.98mins) in paravertebral block group than in control group (41.68±24.96 mins) p<0.001.

CONCLUSION: Preoperative ultrasound guided bilateral paravertebral block using ropivacaine for laparoscopic cholecystectomy is effective for decreasing the additional intraoperative analgesia requirement and prolongs the analgesia duration in postoperative period.

KEY WORDS: *Laparoscopic cholecystectomy, Pain, Paravertebral block, Ultrasound guided*

INTRODUCTION

Laparoscopic cholecystectomy is one of the most commonly performed surgical procedure. Despite of its minimal invasive nature, pain following the laparoscopic cholecystectomy is still the common complain of patient. Origins of pain in laparoscopic cholecystectomy are; somatic, due to multiple port site incision, visceral, due to dissection of calo t's triangle and referred, shoulder pain due to irritation of phrenic nerve. Moderate to severe intensity of pain persists for 3 to 4 days following laparoscopic cholecystectomy, however, pain may remain severe in 10 to 13% of patients throughout the first week.

Ultrasound guided paravertebral block (PVB) is a regional anesthetic technique, where the administration of local anesthetic into the wedge-shaped space on the anterolateral thoracic spine (figure 1). It provides abdominal and thoracic analgesia resulting by ipsilateral somatic and sympathetic nerve blockade in multiple contiguous dermatomes above and below the site of injection. Since the last decade

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ultrasound guided PVB block is emerging technique of pain management strategy in thoracic and abdominal surgery.[9] Parenteral opioids are still a commonly used method to manage postoperative pain after laparoscopic cholecystectomy, but they come with few notorious side effects. Research indicates that bilateral paravertebral block can not only decrease the amount of opioids needed during surgery but also significantly reduces the opioids requirements in post-operative period while maintaining excellent pain relief.[10]

This study aimed to evaluate the analgesic effect of bilateral single level paravertebral block with Ropivacaine in term of intraoperative additional Fentanyl requirement and duration of analgesia in postoperative period in laparoscopic cholecystectomy.

METHODS

This is a clinical observational study that was carried out prospectively in a tertiary care hospital in Nepal between September 2021 and June 2022. The study enrolled 52 patients of American Society of Anesthesiologists Physical Status (ASA-PS) I and II, of both genders, aged between 18-70 years, who were scheduled to undergo elective laparoscopic cholecystectomy under general anesthesia, after obtaining approval from the Institutional Review Board (IRB). Patients with a history of Ropivacaine allergy, coagulopathy, infection at the PVB injection site, and thoracic spine deformity were excluded from the study. A detailed pre-anesthetic evaluation was performed the day before surgery, and patients were provided with informed consent after being informed about the study's purpose and procedure. The patients were informed about the block procedure and the Numeric Pain Score (NPS) 0-10 scale used to assess postoperative pain.The study's sample size was determined based on Agrawal A et al.'s study, which found that patients who received PVB block required less intraoperative additional Fentanyl supplementation than the control group (17.60±19.20 µg vs 38.6±23.16 µg). To achieve a power of 80% and a 95% confidence interval, the study required 26 patients in each group. Group 1 was the PVB block group, in which patients received general anesthesia and ultrasound-guided bilateral PVB block, while Group 2 was the control group that received general anesthesia without PVB block. Patients were instructed to fast for 8 hours before surgery.

Paravertebral nerve block technique: Anesthesiologist performed bilateral PVB block at either T4-5 or T5-6 before inducing anesthesia. The patient was positioned in a sitting position with their chin touching their chest, and a point 2.5-3 cm lateral to the midline was marked on both sides. After preparing the skin with antiseptic, the paravertebral space was located using a 5-10 MHz linear probe (Sonosite M turbo), and the block was performed using a 4" nerve stimulator (Stimuplex; B. Braun AG, Melsungen, Germany) with a plain technique. A small amount of normal saline was injected to confirm the correct space before injecting 20ml of 0.25% Ropivacaine in each paravertebral space. Aspiration was performed after every 5ml injection of Ropivacaine to avoid puncturing vessels or the pleura. The anesthesiologist who had performed at least 10 USG-guided PVB blocks carried out the procedure in the respective operation theater. The fullness of the paravertebral space due to the local anesthetic agent was checked after completing the PVB block. The potential complications associated with paravertebral block, including pneumothorax, hemothorax, vasovagal shock, and local anesthetic toxicity, were carefully observed and managed according to hospital protocol.

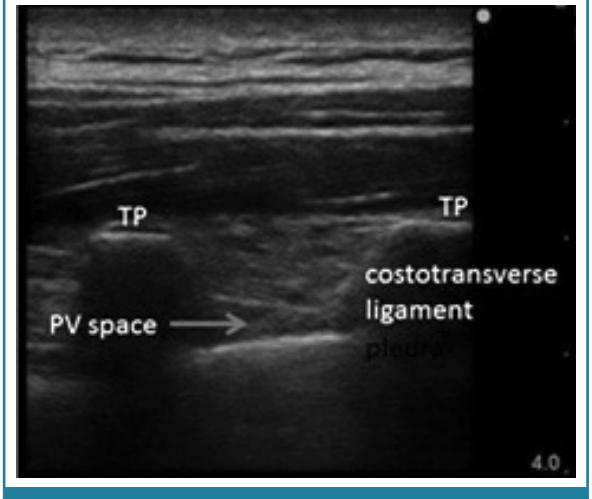

Figure 1. Sonoanatomy of paravertebral space

The anesthesia was induced with a dose of inj. Fentanyl (1.5 µg/kg) followed by titrated doses of inj. Propofol (1-2mg/kg). Tracheal intubation was facilitated by administering inj. Rocuronium (0.8mg/kg). The anesthesia was maintained with oxygen, Isoflurane, and Rocuronium. Intraoperative monitoring was performed using noninvasive blood pressure (NIBP), oxygen saturation (SPO2), electrocardiography

(ECG), and capnography (ETCO2). Additionally, inj. Paracetamol 1gm was administered after intubation. Intraoperative analgesia was provided using inj. Fentanyl (0.5 µg/kg) based on certain criteria such as an increase in heart rate or systolic blood pressure >20%, sweating, tearing, or lacrimation after excluding other causes of sympathetic activation. The number of patients requiring additional intraoperative fentanyl was recorded. A port-side infiltration with 10 ml of 0.25% Bupivacaine was performed at the end of surgery for all patients. Postoperative nausea and vomiting prophylaxis were performed using inj. Ondansetron (4mg). Awake extubation was done after reversal with inj.Neostigmine (0.05mg/kg) with inj. Glycopyrrolate (0.001mg/kg).

The Numeric pain scale (NPS) was used to measure at rest at different time intervals (30min-1hr-2hr-3hr-4hr-8hr-16hr and 24hr) in post operative ward by the attending nursing staff or anesthesia resident doctor. If the patient reported a NPS score of greater than 3, rescue analgesia (Inj. Ketorolac 30mg IV) was given. The time from the end of surgery to the first rescue analgesia was noted as the time of rescue analgesia. No background analgesic agent was given until the time of first rescue analgesia. The primary objective of the study was to determine the time of first rescue analgesia, while the secondary objectives were to assess the intraoperative additional Fentanyl requirement and any side effects of PVB.

The data collected was analyzed using the independent samples t-test for numerical data (age, height, weight, duration of surgery, time for first rescue analgesia) and chi-square test for categorical data (ASA PS, gender, additional intraoperative Fentanyl requirement) with the help of the Statistical Package for Social Studies (SPSS -21). The results were reported as mean ± standard deviation (SD) or number (n) and percentage (%). A p-value of < 0.05 was considered statistically significant.

RESULTS

In this clinical prospective observational study, a total of 52 patients were initially enrolled. However, three patients from group 1 developed vasovagal shock during paravertebral block, and one patient in group 2 converted to open surgery. The demographic details including age, gender, weight, and ASA PS, as well as the surgery duration, were comparable between the two groups (p>0.05), as demonstrated in table 1.

Table 1. Patient characteristics and operation time

Variables	Group1(23) Mean±SD	Group2(25) Mean±SD	p value
Age (years)	43.56±12.74	45.64±10.64	0.54
Weight(kg)	61.43±9.40	62.24±7.80	0.74
Gender(M/F)	6/17	7/18	0.88
ASA PSI/II	15/8	17/8	0.83
Operation time (min)	76.47±20.43	67.76±20.43	0.11

In group1, none of the patient required additional dose of fentanyl during intraoperative period where as in group2, 15.38% (4 / 25) patient required additional intraoperative fentanyl, which was statistically significant (p=0.045) shown in table 2.

Table 2. Intraoperative additional analgesia

Intraoperative additional fentanyl (n/%)	Group1 (23)	Group2 (25)	p value
	0/23(0%)	4/25(15.38%)	0.045

Time for first rescue analgesia was longer in group1 (161.26 ±138.98 mins) than in group2 and (41.68 ±24.96 mins) which was highly statistically significant, p<0.001 shown in table 3.

Table 3. Time of first rescue analgesia

Time of first rescue analgesic (Mean±SD)	Group1(23)	Group2 (25)	p value
	161.26± 138.98mins	41.68± 24.96mins	<0.001

DISCUSSION

Multimodal approach of pain management is required to control intra and postoperative pain following laparoscopic cholecystectomy. Ultrasound guided bilateral preoperative paravertebral block is one of the effective and safe method of multimodal approach of pain management. Since the opening of ports are in both side of abdomen and pain discomfort due to pneumoperitoneum is diffuse in nature so we aimed to performed and access the effect bilateral PVB . Ultrasound also helped to visualize the spread of injected drug in paravertebral space whereas in landmark and PNS guided approach of PVB, multiple level of injection on same side, partial or fail block and chances of pneumothorax is higher than ultrasound guided block. To the best of our knowledge, our study is the first study in our setup to evaluate the analgesic effect of bilateral ultrasound guided PVB block in patient undergoing laparoscopic cholecystectomy.

None of the patients in group1 required additional Fentanyl during intraoperative period, while 4 out of 25 patients (15.38%) in group 2 required extra fentanyl, p=0.045. The time for first rescue analgesia was significantly longer in group 1 (161.26 ±138.98 mins) compared to group 2 (41.68 ±24.96 mins), p <0. 001.In our study, we found that in ultrasound guided bilateral paravertebral block group, none of the patient required additional intraoperative analgesics. Aydin G et al[8] (2018) compared the ultrasound guided unilateral PVB with 20ml of 0.5% bupivacaine and found none of the patient in PVB group (0/30) required additional analgesia during intraoperative period. Their study have shown even unilateral ultrasound guided PVB is effective as one of component in multimodal intraoperative pain management approach. Agrawal A et al. (2012) found that, 11 out of 25(44%) did not required additional analgesic PVB group where as in control group only 4 (16%) didn't required additional intraoperative analgesics. The requirement of additional analgesic is lesser in PVB group. However higher percentage of patient needed additional analgesic in PVB in comparison to our study (0 vs 44%).This difference is likely due to ultrasound guided block technique used in our study which not only make it easy to confirm the paravertebral space but also helps to visualize the drug spread to different level of paravertebral space. None of the patient required additional intraoperative analgesia in ultrasound guided PVB (unilateral) group in study done by Gündost L et al (2020). Similar results of paravertebral block have been shown in laparoscopic, open abdominal and thoracic surgeries.[4, 5]

Agrawal A et al[9] (2012) found mean time for first rescue analgesia time was 270 mins which is longer than our study (161minutes) despite of they have performed unilateral (right sided) ultrasound guided PVB. Study done by Fentie D et al mean analgesia time in postoperative analgesia in unilateral PVB (landmark) group was 120 minutes and 30 minutes in control group. They have only included the patient after success of the PVB was confirmed. Kamhawy G et al compared ultrasound guided PVB with subcostal TAP block in laparoscopic cholecystectomy. They have found mean duration of first analgesia was significantly longer in PVB group (432 mins).Use of higher concentration 0.5% of 20 ml bupivacaine (in our study we used 0.25% ropivacaine) could be the reason for prolong duration of analgesia than in our study. In group1, there was no additional requirement of intraoperative fentanyl and prolonged analgesia time in postoperative period indicates that pre-incisional PVB block also poses the preemptive analgesic effect in patient undergoing laparoscopic cholecystectomy.

Complications like pneumothorax, hematoma, epidural or intrathecal spread and vasovagal shock have been reported during thoracic paravertebral block. These complications are higher in landmark and PNS guided technique than in ultrasound guided block. In our study, none of the patient developed hematoma, pneumothorax, hemothorax but two of the patients in PVB group developed vasovagal shock during the block. One of them had dizziness, hypotension followed by bradycardia and treated with fluid bolus and inj.Mephentermine and other patient had dizziness and hypotension. Both of them were young female and last case of the list. In both the cases blood sugar level (by glucometer) was in lower side (73mg/dl and 87mg/dl). Multiple confounding factors like prolonged nil per oral, lower blood sugar level, not using any anxiolytic and systemic analgesic agent during PVB block could have been potentiated the vasovagal shock. Similar incidents during PBV have been also noticed by Agarwal s el al and Yaman F during PVB block.

LIMITATION

A limitation of our study is that we did not assess the extent of dermatomal coverage achieved by the block.

CONCLUSION

Preoperative ultrasound guided bilateral paravertebral block using Ropivacaine for laparoscopic cholecystectomy is effective for decreasing the additional intraoperative analgesia requirement and prolongs the analgesia duration in postoperative period.

RECOMMENDATION

Based on this study, ultrasound-guided paravertebral block appears to be a good option for pain management during and after laparoscopic cholecystectomy. However, further research in the form of larger randomized controlled trials is necessary to fully establish its efficacy and safety.

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Original Article

Physical Activity Level in Patients with Knee Osteoarthritis Visiting Dhulikhel Hospital: A cross sectional study.

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ABSTRACT

INTRODUCTION: Physical activity is an important public health intervention to improve the health of persons with arthritis. Because of pain on mobility, Patient with knee osteoarthritis may be physically inactive as compared to population without osteoarthritis.

OBJECTIVE: The objective of this study was to identify the level of physical activity in patients with knee osteoarthritis.

METHOD: Patients with knee osteoarthritis meeting the clinical diagnostic criteria given by American college of Rheumatology were interviewed. Then physical activity of patient with knee osteoarthritis was classified into light, moderate and vigorous using global physical activity questionnaire. Nepali-version of numeric pain rating scale was also used in order to measure the pain intensity which was further classified into mild, moderate and severe pain. Data were further analyzed to find out the correlation between two measures.

RESULT: Out of 78, Patients with knee osteoarthritis, 19(24.4 %) were male and 59(76.6%) were female.79.5% of patient with knee osteoarthritis are involved in moderate level of physical activity. Among the knee osteoarthritis patient 16.7% had mild pain, 76.9% had moderate pain and 6.4% had severe pain.

CONCLUSION: Most of the knee osteoarthritis patients were involved in moderate level of physical activity. Work-related domain of physical activity contributed more to total physical activity as compared to leisure-time physical activity. And we found that there is no association between level of pain and physical activity in knee osteoarthritis patient.

KEY WORDS: *Function, Knee, Osteoarthritis, Pain, Physical activity*

INTRODUCTION:

Knee osteoarthritis (KOA) is a degenerative joint disease which involves the cartilage and surrounding tissues of the knee joint which leads to physical disability with advancing age.[1] It is not a disease of cartilage alone but also affects the whole joint, including articular cartilage, meniscus, ligament, and peri-articular muscle.[2] Patient with knee osteoarthritis often complains of pain and joint stiffness of affected extremity.[3] Because of pain on mobility, patient with knee OA may be physically inactive as compared to population without osteoarthritis.[4]

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Physical activity(PA) broadly encompasses exercise, sports and physical activities done as part of daily living, occupation, leisure and active transportation.[5] Physical activity provides many health benefits; reduce the risk of chronic diseases such as hypertension, diabetes, stroke, and cancer. Similarly, it promotes healthy cognitive and psychosocial function.[6] Not only this, considerable research suggest that patient with KOA who were physically more active complained of less pain as compared to those who were physically less active.[7,8]

European League against Rheumatism (EULAR) guidelines recommends that patient with knee osteoarthritis should engage in joint-friendly regular moderate to vigorous physical activity (aerobic; moderate: at least 150 min per week, or vigorous: at least 75 min per week, or a mixture of both, on at least five days a week summed to ≥600 MET-min/week best performed in bouts of at least 10 min.[9] According to the

National health interview survey patient with arthritis were less physically active. More than 37% arthritic population is inactive in US.[10] Similarly, another study done in U.S. found that only 12.9% of men and 7.7% of women with radiographic knee osteoarthritis has met the recommended guidelines of physical activity. So, nowadays physical activity is considered as an important public health intervention to improve the health of persons with arthritis.[11]

However, there have not been any reported data about the physical activity status in patient with knee osteoarthritis in South Asian countries although several western studies reported of less physical activity in KOA which indicated the further need of study.

METHODS:

This observational cross-sectional study was carried out in the 78 patients with knee osteoarthritis visiting orthopedics and physiotherapy OPD. Non probability convenience sampling method was used and sample size was calculated using formula z^2pq/e^2.

Individuals with knee pain visiting physiotherapy outpatient department and orthopedics department were screened using on American college of rheumatology clinical diagnostic criteria. American college of rheumatology clinical diagnostic criteria consists of following criteria.

1. age≥ 50,
2. morning stiffness > 30 minutes,
3. bony tenderness,
4. bony warmth,
5. bony enlargement and
6. Crepitus.

Patient with knee pain presenting at least three of above mentioned six criteria were considered as eligible participants. Eligible participants were provided a subjective information sheet explaining the objective of the study, benefits, harms, right to withdraw, time taken to complete the form and confidentiality. After the participants agreed to participate, written and verbal informed consent was taken from every participants. People who didn't give consent were excluded from this study. Those who gave consent were interviewed Nepali version of numeric pain rating scale (NPRS-NP) and global physical activity questionnaire(GPAQ). GPAQ was analyzed using GPAQ analysis guide and physical activity was categorized as low, moderate and vigorous physical activity and pain intensity was classified as mild,moderate and severe[12–14] moderate, and severe pain in terms of pain-related interference with functioning in patients with chronic musculoskeletal pain, to measure the variability of the optimal cut-offpoints, and to determine the influence of patients' catastrophizing and their sex on these cut-offpoints. Methods: 2854 patients were included. Pain was assessed by the NRS, functioning by the Pain Disability Index (PDI. The demographic data of participants was recorded.

GPAQ collects information on physical activity participation in three settings (or domains) as well as sedentary behavior, comprising 16 questions. The domains are activity at work travel to and from places, recreational activities.It has good test-retest reliability.[15] Numeric pain rating 11-point scale for patient self-reporting of pain where 0 means "no pain" and 10 means "worst imaginable pain." It is used for assessing pain severity. It has good internal consistency and test-retest reliability[16] the objectives of this study were to translate and cross-culturally adapt the NPRS and GROC into Nepali and to assess the psychometric properties of the Nepali version of the NPRS (NPRS-NP.

The data collected was tabulated and analyzed by using the Statistical Package for Social Sciences(SPSS) version 23. Findings were described in terms of percentage. Chi-square test was used to see the association between pain intensity and physical activity level.

RESULTS

Characteristics of study sample

The demographics parameters of participants are summarized in table 1. The mean age of patient with knee osteoarthritis was 56 years. The maximum numbers of patients were in age group 61-70 years. Female patients with knee osteoarthritis were more than male patients. Most of the patients with knee osteoarthritis were housewife which is then followed by involvement in agriculture. More than half of the populations were married.

Most of the patients with knee osteoarthritis were involved in moderate level of physical activity. But total PA was mostly contributed by work related and travel related domain of PA as compared to leisure time PA. (Table 2)

Table 1: Distribution according to demographics	
Characteristics	**Total Sample (n=78)**
Sex	**n(%)**
Male	19 (24.4)
Female	59 (76.6)
Age range (yrs)	
31-40	7 (9)
41-50	19 (24.4)
51-60	19 (24.4)
61-70	26 (33.3)
71-80	6 (1.7)
81-90	1 (1.3)
Occupation	
Self-employed	14 (17.9)
Government job	3 (3.8)
Housewife	32 (41)
Agriculture	29 (37.2)
Marital status	
Married	69 (88.5)
Widow	9 (11.5)
Ethnicity	
Newar	25 (32.1)
Brahmin	20 (25.6)
Chhetri	7 (9)
Tamang	12 (15.4)
Magar	5 (6.41)
Others	9 (11.5)

Table 2: Domain specific contribution to total PA, WHO recommended PA along with achieved physical activity leve				
MET min of PA in a week	**Mini-mum**	**Maxi-mum**	**Mean**	**Standard deviation**
Work	0	12960	2160	2970.966
Travel	360	8400	3460	1599.734
Recreational	0	3360	406.15	642.514
Total	840	16320	6026.15	3463.808
Level of physical activity			**n(%)**	
Low			NA*	
Moderate			62 (79.5)	
Vigorous			16(20.5)	

The average pain intensity was 5.19. And about 3/4th patients with knee osteoarthritis experienced moderate pain. And, association between pain and physical activity was statistically not significant. (Table 3)

Table 3: Distribution by pain severity and association between physical activity and pain severity			
	Pain Severity		
	Mild Frequency (%)	**Moderate Frequency (%)**	**Severe Frequency (%)**
Physical Activity			
Low	NA*	NA*	NA*
Moderate	8 (10.3)	50 (64.1)	4 (5.1)
Vigorous	5 (6.4)	10 (12.8)	1 (1.2)
Chi-square test			**p-value**
Correlation between Pain and physical activity			0.21*
*Not significant			

DISCUSSION:

This cross-sectional aimed to identify the level of physical activity and the extent to which physical activity is affected by pain severity in patients with knee osteoarthritis. This study found that most of the patient with knee osteoarthritis is involved in moderate level of physical activity. In addition, all the patients included in this study met the recommended guidelines of physical activity in arthritic population. Various studies about physical activity level on healthy population in Nepal also showed higher physical activity as compared to studies done in other countries[17,18] low- and middle-income countries. Nepal, a low-income country in South Asia, is undergoing an epidemiological transition. Although the reported national prevalence of physical inactivity is relatively low, studies in urban and peri-urban localities have always shown higher prevalence. Therefore, this study aimed to measure physical activity in three domains-work, travel and leisure-in a peri-urban community and assess its variations across different sociodemographic correlates.Methods: Adult participants (n = 640. And about 3/4th population with knee osteoarthritis complained of having moderate pain. Current study showed that the proportion of patients involved in physical activity decreases with increasing age which is similar to other studies. Ramires VV et al and Buchman et al found that with increasing age, there is decrease in physical activity[19,20] potentially influencing quality of life, incidence of diseases and premature mortality. The aim of this study was to describe objectively measured physical activity levels among older adults residents in a Southern city of Brazil. Methods: A population-

based study was carried out including people aged 60+ years living in the urban area of Pelotas. Face-to-face interviews, anthropometric measures and triaxial accelerometry (non-dominant wrist.

Physical activity level in the current study is higher than the previous studies conducted in different countries. Shim HY et al found that 61.1% were inactive and 25.9 % were minimally active in patient with knee osteoarthritis in Korea(21)1279 participants aged ≥50 years who had radiographic KOA and who evaluated knee pain on a numerical rating scale were selected. KOA was assessed using the Kellgren-Lawrence system. The Korean short version of the International Physical Activity Questionnaire was used to measure physical activity status. We used the physical activity recommendations of the American College of Rheumatology Work Group Panel when evaluating the extent of activity in KOA patients. Results: Only 18.6% of KOA patients met the osteoarthritis expert panel recommendations, lower than in the general population (23.2%; p=0.003. Similarly,another study done in united states found that only 23.6% of population with knee osteoarthritis were involved in moderate physical activity and 0.95 % were involved in vigorous physical activity.[22] The percentage of population meeting the recommended guidelines for physical activity in knee osteoarthritis is also higher than previous studies done in different countries, in US, only 12.9% of men and 7.7% of women with radiographic knee osteoarthritis have met the recommended guidelines of physical activity and in Korea, only 23.4% had met the recommended guidelines.[11,21] 1279 participants aged ≥50 years who had radiographic KOA and who evaluated knee pain on a numerical rating scale were selected. KOA was assessed using the Kellgren-Lawrence system. The Korean short version of the International Physical Activity Questionnaire was used to measure physical activity status. We used the physical activity recommendations of the American College of Rheumatology Work Group Panel when evaluating the extent of activity in KOA patients. Results: Only 18.6% of KOA patients met the osteoarthritis expert panel recommendations, lower than in the general population (23.2%; p = 0.003.

Variation in level of physical activity in our study might be due to factor affecting physical activity. Different studies have found that differences in infrastructures, occupational variation as well as geographical variation, temperature variation and countries' national income are responsible for differences in physical activity level. Higher physical activity in our study may be due to occupational activity because more than half of the patients were involved in agriculture and household activities which require more manual labor.[23–25] According to WHO, countries with lower national income had higher physical activity as compared to countries with higher national income.[26] These result contrast from the study by Kari JT et al and Armstrong S et al. In their study, they found that people with higher income tend to have gym membership and more physical activity facility resulting in higher physical activity.[27,28] One study found that countries with lower national temperature have more moderate to vigorous physical activity and vigorous physical activity(29). In contrary, other studies found that increase in temperature increases physical activity.[30–32]

Together our result found that most of the people with knee osteoarthritis are involved in moderate level of physical activity because many of them are involved labor intensive occupation. Work-related domain of PA contributed more to total PA as compared to recreational domain of PA. Increase in temperature, low annual income, occupation and social support are the factors facilitating physical activity.

There are some limitations in our study. First, we use a self-reported questionnaire to know about a physical activity level which may result in information bias. Second, instead of activity monitors such as accelerometers to measure physical activity, we used self-reported GPAQ. However, GPAQ is a valid tool for assessing physical activity level.[15] There might be possibility of participants' inability to recall events 7 days prior to data collection while responding to the questions on GPAQ. Third, the result couldn't be generalized to whole population because sample size is small due to time limitation during data collection.

CONCLUSION:

In our study, most of the patients with knee osteoarthritis were engaged in moderate level of physical activity which is followed by vigorous physical activity. But total physical activity in our study was mostly contributed by work-related physical activity. Hence in clinical setting, patients with knee osteoarthritis should be encouraged to involve in leisure-time physical activity which will have positive

effect on pain, physical function, mental health and health related quality of life. Similarly, association between pain and physical activity was statistically not significant.

RECOMMENDATION

This study recommends to examine whether patient with knee osteoarthritis are involved in appropriate and joint-friendly physical activity or not by using objective measure of physical activity.

LIST OF ABBREVIATIONS

PA: Physical activity
OA: Osteoarthritis
KOA: Knee osteoarthritis
GPAQ: Global Physical Activity Questionnaire
MET: Metabolic Equivalent
NPRS-NP:Nepali version of Numeric Pain Rating Scale
SPSS: Statistical Package for Social Sciences
WHO: World Health Organization
EULAR: European League against Rheumatism
OPD: Out-patient Department

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Prevalence and Awareness of Diabetic Retinopathy among Known Diabetic Patients Visiting the Sagarmatha Chaudhary Eye Hospital, Lahan

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ABSTRACT

INTRODUCTION: Diabetic retinopathy causes irreversible blindness. Most of the patients visiting the hospital have no signs and symptoms until too late for effective treatment. Early diagnosis and treatment are important to prevent blindness due to diabetic retinopathy.

OBJECTIVE: The study aimed to assess the awareness regarding diabetic retinopathy, the prevalence of diabetic retinopathy among diabetic patients, and its association with demographic characteristics.

METHOD: The hospital-based analytical cross-sectional study at Sagarmatha Choudhary Eye Hospital from Feb 2018 to Dec 2018. Pretested tools were used to collect the data. Bivariate analysis was done using SPSS 20 version.

RESULT: A total of 303 participants was included in the study. The mean age of the participants was 53.9(±10.2) years. The prevalence of diabetic retinopathy was 72%. Among known diabetic patients, were 85(28%) had clinically significant macular edema, 51(16.8%) had Proliferative diabetic retinopathy, 38 (12.5%) had Mild non-proliferative diabetic retinopathy, 31(10.2%) had moderate non-proliferative diabetic retinopathy, 14(4.6%) had severe non-proliferative diabetic retinopathy and 84 (27.7%) had no DR. The odds of having diabetic retinopathy among knowing diabetic Mellitus was 1.59 times in comparison to no knowledge (95%CI: 0.93,2.7; p value=0.04). The reason for late coming to eye examination was less awareness 57%.

CONCLUSION: The prevalence of diabetic retinopathy was 3 in 4 among diabetic patients. Awareness regarding diabetic retinopathy was poor. There is a need to develop an awareness program on diabetic retinopathy among known diabetic patients.

KEY WORDS: *Awareness; Diabetic retinopathy; Eye Hospital; Nepal*

INTRODUCTION

There are approximately 463 million people in the world living with diabetes.[1] Diabetic retinopathy(DR), the leading cause of vision loss and blindness in adults 20–74 years of age[2] is preventable and treatable.[3] A systematic review and meta-analysis shows that the global prevalence of Diabetic Retinopathy, Proliferative Diabetic Retinopathy (PDR), and Non-Proliferative Diabetic Retinopathy (NPDR) among Type 2 Diabetic Mellitus (DM) patients were 28%, 6%, and 27% respectively; while the prevalence of PDR and NPDR in DR patients were 17% and 83% respectively.[4] World Health Organization (WHO) has estimated that diabetic retinopathy is responsible for 4.8% of the 37 million cases of blindness throughout the world.[5] Currently, cataracts and refractive error are responsible for most of the visual impairment in Asia, although diabetic retinopathy causes 3% to 7% of the total blindness throughout the region.[6] The

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hospital-based study showed a 78% prevalence of DR among known DM in Nepal [7] and 21% at Patna Medical College, Bihar.[8] A recent community-based study done at Kathmandu showed the prevalence of DR among patients with DM to be 19.4%.[9] Bhaktapur's study showed that the prevalence of DR was 23.8% among persons with diabetes.[10] A major reason behind this high prevalence is the lack of awareness among the patients who fail to achieve a timely diagnosis and medical attention.[11] Moreover, 37% were unaware of diabetic retinopathy.[12] which leads to an increase in the prevalence of blindness due to Diabetic retinopathy. A diabetic patient is 25 times more vulnerable to the possibility of getting blindness as compared to a healthy individual.[13] Diabetic eye disease often has no early signs and symptoms. The typical standard of care for diabetic patients is to receive an annual dilated fundus examination and screening for Diabetic retinopathy. Unfortunately, only about half of patients with diabetes visit the eye specialist for annual retinal exams.[14]

Sagarmatha Choudhary Eye Hospital (SCEH) has been providing Vitro Retinal Services to needy people. Still many patients visiting the Vitro retinal department are in the late stage of DR at presentation and were unaware of their problem.

The objective of the study was to assess the awareness regarding diabetic retinopathy, the prevalence of DR among diabetic patients, and find out the reason for the late presentation among diabetes patients visiting SCEH.[15] This finding will be useful for the eyecare providers to know the common status and prevalence of DR among the presenting patients and formulate treatment plans as well as counseling plan for the patients.

METHODS

Study design: The hospital-based analytical cross-sectional study

Setting: The present study was carried out in the Sagarmatha Choudhary Eye Hospital, Lahan which is located in South-East Nepal (Province 2), at the East-West Highway close to the Indian border, neighboring the Indian state Bihar. The hospital was led by renowned ophthalmologist Dr. Albrecht Hennig, a German doctor working at Lahan for more than 3 decades for the prevention of blindness. The hospital provides more than 50,000 sights restoring surgery every year. In 2017, more than six hundred diabetic patients visited the VR department and among them 323 patients were treated with Retinal Laser. This hospital-based study was done at Sagarmatha Choudhary Eye Hospital from February 2018 to December 2018 in Lahan, Nepal.

Participants: The study subjects were all consecutive new diabetic patients attending the vitreoretinal department and willing to participate. Patients with a history of prior intervention for diabetic retinopathy such as laser therapy and surgical intervention were excluded from the study.

Ethical Consideration: The study was conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained from the patients before enrollment in the study. Approval was taken from the IRC of NNJS Reg. no. ER-9.5/2021 for the conduction of the study.

Outcome Variables: Presence of Diabetic Retinopathy. Each fundus photograph was graded lesion by lesion, and the severity of retinopathy was determined using the proposed new international classification of diabetic retinopathy. Diabetic retinopathy was classified into five severity levels: (1) no retinopathy, (2) mild non-proliferative, (3) moderate non-proliferative, (4) severe non-proliferative, and (5) proliferative diabetic retinopathy (PDR). Diabetic macular edema was classified as clinically significant macular edema (CSME) or non-CSME, based on the Early Treatment Diabetic Retinopathy Study criteria. The eye having severe problems was selected for the analysis.

Data sources/ Measurements: The data was collected by the trained single Ophthalmic assistant of the retina department. All the data was entered into the excel sheet, data processing coding was done by using SPSS (Statistical Package of Social Sciences) version 17 (developed by IBM crop).

Bias: The pre-testing of tools was done and modification was made. The expert opinion was taken to finalize the tools. The questionnaire was translated into Nepali language and Maithili language was also used for an interview, to ensure that patients fully understood each question.

Study size: 303 patients from February to December 2018. A purposive sampling method was used.

Quantitative variables: Detailed demographics, education status, occupation, family income, family type, awareness of potential ocular problems from diabetes mellitus, family history of diabetes mellitus, duration of diabetes mellitus, and presence of hypertension. Awareness of DM, awareness on DR, the presenting and best-corrected Snellen visual acuities was recorded. Detailed fundus evaluation was done after pupil dilation. Visual acuity (VA) was measured in both eyes by trained research optometrists using a Snellen E chart. Retinopathy was classified according to early treatment of diabetic retinopathy study (ETDRS) classification[16]. The WHO categorization was done for visual acuity. For analyzing the data, the eye having severe problems was selected for the study. Anterior segment examination was done by tabletop slit lamp (APPASAMY) model AIA 11 2S.

Statistical methods: For continuous data, mean and the standard deviation was calculated and binomial logistic regression and multivariate analysis were done to see the significance of association. Odds ratio was calculated at 95% confidence interval and p-value <0.05 was considered as significant level.

RESULTS

A total of 303 participants participated in the study. The numbers of males were 95 (31.4%), and females were 208 (68.6%). The demographic data showed that 67.3% were from India, 255 (84%) were Hindu religion, 91 (30%) were illiterate, 87(28.7%) were housewives, 155(51.2%) were of joint family. The mean age of the participants was 53.9(±10.2) years. The median family income was 16000 (IQR:9000,32000), the median number of years since diagnosis of DM was 5(IQR:2,10), 253 (83.5%) were above the poverty line. (Table 1)

Awareness and practice regarding DR among the patients visiting the VR department of Sagarmatha Choudhary Eye Hospital

The majority (90%) used regular medicine for DM control, 96% said they took medicine by consulting a general physician. While asking regarding diabetes control, 70% said their diabetes was under control but when asking what is the effect of diabetes on health 63% answered they don't know and 71% were unaware on the effect of diabetes on the retina. The majority (73%) had heard about the retinal service of SCEH. (Table 2)

Association of DR with demographic characteristics

The odds of having DR among females is 1.89 (95%CI:1.12,3.2; p value=0.00) times compared to males. The odds of having DR among one-year older population was 1.014 times the odds of having DR among one year younger participants (95% CI: 1.01,1.06). The odds of having DR among Indian patients is 1.39(95%CI: 0.83,2.36; p value=0.59) times compared to Nepal. The odds of having DR and Hinduism is 0.963 (95%CI: 0.48,1.92; p value=0.55) times compared to the Muslim religion, the odds of having DR among illiterate is 1.83 times compared to literate (95% CI:1.01,3.31; p value=0.01), the odds of having DR among nuclear family is 0.88 times compared to the joint family(95%CI: 0.53,1.45;p value=0.162), the odds of having DR among above poverty line is 1.91 times (95%CI: 0.88,4.14; p value=0.44) The odds of having DR among known diabetics was 1.59 times in comparison to no knowledge (95%CI: 0.93,2.7;p value=0.04) Similarly, the odds of having DR among known diabetics was 1.5 times in comparison to no knowledge on DR (95%CI: 0.88,2.58;p value=0.19). The odds of having DR among having a history of HTN was less likely to 0.47 in comparison to no history of HTN (95%CI: 0.28,0.78; p value=0.11), The odds of having DR among the family history of DM is less likely to those having no history of DM (95% CI:0.37,1.13; p value=0.16). The odds of having DR among the duration of diabetes >10 years is 2.68 times in comparison to <10 years (95% CI:1.33,5.38; p value=0.01).

The multivariate logistic regression analysis showed that the odds of having DR are significantly associated with gender, age, education, knowledge of DM, and duration of DM. (Table 3)

The prevalence of diabetic retinopathy was 72(95% CI: 66.9, 77.2). (Figure 1)

Among known diabetic patients, 85(28%) had clinically significant macular edema, 51(16.8%) had Proliferative diabetic retinopathy, 38 (12.5%) had Mild non-proliferative diabetic retinopathy, 31(10.2%) had Moderate non-proliferative diabetic retinopathy, 14(4.6%) had Severe non-proliferative diabetic retinopathy and 84 (27.7%) had no DR. (Table 4)

Uncorrected visual acuity was found to be normal in31.5% and blindin 26.9% in the right eye which improved after refraction to normal (37.4%), and blind

(26%). Similarly, uncorrected visual acuity was found to be normal in 32%, blind in 22.8% in the left eye which improved after refraction to normal in 41% and blind in 22.4%. (Fig 2)

While asking the reason for late coming for eye examination, 57% said they had less awareness about eye examination, 28% said they were under treatment at other eye hospitals and 15% did not respond. (Fig-3)

DISCUSSION

In this hospital-based study, the awareness on DR was found to be poor, the prevalence of diabetic retinopathy was 3 in 4 among known diabetic patients visiting SCEH, Lahan. Regarding the stage of DR, majority had clinically significant macular edema. DR was seen more in females compared to males. The reason for the late presentation was having less awareness about the disease.

The awareness on DR was 29% in this study, which is less than the study done in Ethiopia 47%.[17] The global prevalence of DR among diabetic patients was 34.6% (95% CI 34.5–34.8) for any DR.[18] The findings of this study show that the prevalence of DR among known diabetic patients was 72% (95% CI: 66.9, 77.2) which is similar to the study done at Tilganga Institute of Ophthalmology, which shows 78% had DR,[7] other studies show 44%,[19] 49% in India, 50% in Kenya study and 21% in Patna study.[8] Similarly, the community-based study showed the prevalence of DR to be 16.[20] The pathogenesis of DR is multifactorial but is primarily due to the metabolic effects of chronic hyperglycemia, which result in dramatic vascular changes and subsequent retinal injury and ischemia.[21] Most of the patients have no signs and symptoms until it's too late for effective treatment.

The educational level of the participants in this study is also low (30% were illiterate and 26% were of primary level) which is similar to findings seen in the study done at Tilganga Institute of Ophthalmology by Thapa et al. (more than half were unable to read and write)[7]

In this study, clinically significant macular edema was found in 85(28%) of DR cases in contrast to the study done in India which showed 51%.[22] The community-based study done at Dharan showed 3.8% cases of CSME.[23] Similarly, in this study 51(16.8%) had Proliferative diabetic retinopathy but the study done at Patna showed 28.6%.[24] This shows that most of the patients presenting to our hospital are at an advanced stage of DR.

In this study, the association of DR with gender, country, education, and time duration of diabetes mellitus was statistically significant while religion, history of HTN, family history of DM was not statistically significant.

The trained staff collected data and fundus evaluation was done by an Ophthalmologist. The study was hospital-based and might not be generalized for the general community. Despite this, it is important to counsel patients visiting for eye examination regarding the importance of regular examination of the eye, screening, early diagnosis, and treatment of Diabetic retinopathy to reduce the global burden of blindness due to diabetic retinopathy.

CONCLUSION:

The study concludes that the prevalence of DR among known diabetic patients is very high. Most of the patient's visits were at the late stage of DR. The reason for the late presentation was having less awareness. Hence there is a need to increase awareness regarding DM and DR among the patients visiting hospitals and in the general community.

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A Case-control Study on the Correlation between the Ovarian Reserve Test and Thyroid Hormone Levels at the Paropakar Maternity & Women's Hospital

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ABSTRACT

INTRODUCTION: One in every four couples are affected with infertility in the developing countries. The situation of infertility is increasing in Nepal and it needs to be addressed.

METHOD: A single-center case control study was conducted at the Paropakar Maternity & Women's Hospital between April 14th, 2023 to June 25th, 2023. A total of 133 patients were enrolled for the study. All patients, between 20-40 years, who had spontaneous menstrual cycles on days 2 or 3 visited the OPD were included in the study. However, the patients who had cases such as endometrosis, ovarian surgery for ovarian cysts and ovarian tumors, under chemotherapy treatment and hormonal treatment, and polycystic ovary syndrome were excluded in the study.

RESULT: This study aimed to investigate the relationship between ovarian reserve test and thyroid hormone level in women with infertility. Two groups were divided on the basis of the TSH level, control (TSH<4.5) and case (TSH≥4.5). Based on the findings of the study of Pearson's correlation test, AMH and FT4 were found to be statistically significant and have moderate positive relationships for the case group, which suggests that, with increase in level of AMH, FT4 also tends to increase. In addition, Spearman's correlation test was used to further explore the non-linear relationship, which helped to establish the positive significant correlation in the control group between AMH and FT3.

CONCLUSION: Based on the findings of the study of Pearson's correlation test, AMH and FT4 were found to be statistically significant and have moderate positive relationships.

KEY WORDS: *Infertility, Nepal, Ovarian Reserve Test, Thyroid hormone*

INTRODUCTION:

Infertility is a condition of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. According to WHO study, one in six couples globally, or 17.5% of the adult population, suffer from infertility, demonstrating the urgent need to expand access to high-quality, reasonably priced fertility care for individuals who are in need[1]. Although infertility does not have a life-threatening complication, it has significant impacts on the health of an individual like depression, anxiety, domestic abuse, stigma, sexual dysfunction and social isolation but it has received a limited attention. Infertility has been an emerging issue worldwide and it is prevalent also in the scenario of Nepal. The districts of Rautahat has lowest 8.1% and Kapilvastu have the highest frequency of 14.9% infertility issues[2]. Between the male and female infertility, females are more stigmatized and exposed to cases of infertility.

In the case of female fertility, ovarian reserve is one of the important factor. It can be evaluated with serum biomarkers and transvaginal ultrasound tests. Serum biomarkers are serum Anti-Mullerian Hormone (AMH)

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and Follicle Stimulating Hormone (FSH). Another reliable marker for ovarian reserve test is measurement of Antral Follicle Count (AFC) which is done by using transvaginal ultrasound. Serum AMH has no diurnal and intra- and inter-cycle variability; therefore, it is considered as a sensitive marker of ovarian aging and ovarian reserve[3]. Transvaginal ultrasound assessment of AFC provides direct estimation of the recruitable follicle. Although counting the resting basal antral follicles is an operator dependent procedure, it still considered as a sensitive marker for ovarian reserve and should be done on day 2-3 of the menstrual cyccle[4]. Other sensitive biomarker for Ovarian reserve test is Basal serum Follicle Stimulating Hormone (FSH) measured on day 2 and day 3 of the menstrual cycle. However, it is known to have diurnal, intra- and inter-cycle variability [5,6].

Thyroid disorders are one of the most common endocrine problems in reproductive age and may cause menstrual and ovulation disorders and infertility. It plays an important role in the development and differentiation of all cells of the human body including granulosa cells and oocytes in female reproductive system. It enhances the granulosa cell proliferation and inhibits granulosa cell apoptosis. Thyroid dysfunction can cause ovulatory dysfunction, menstrual irregularities, subfertility and recurrent miscarriage[7]. Although some studies has shown the conflicting results between the relationship with thyroid hormone and ovarian reserve but the number of studies has supported the association between high serum TSH level and decreased ovarian reserve [8,9].

The objective of the present study is to investigate the relationship between thyroid hormone levels and ovarian reserve test.

METHODS:

This section details the methods used for the research. This single-center, case-control study was conducted at Paropakar Maternity & Women's Hospital (PMWH) in Kathmandu, Nepal, between 14th April 2023 to 25th June 2023. The study participants who visited the Outpatient Department (OPD) during the allotted period were included in the study. PMWH was established in 1959 A.D and is the first maternity hospital in Nepal. It is a tertiary care hospital with 415 beds.

A total of 211 patients who had spontaneous menstrual cycles on days 2 or 3 visited the OPD during the study duration were included in the study. Out of 211, only 133 patients were deemed eligible for inclusion. The remaining 78 (endometrosis-13, ovarian surgery 5, ovarian cysts 10, under chemotherapy treatment-4, hormonal treatment-18, and polycystic ovary syndrome-28) were excluded. Of the 133 patients enrolled, 93 were enrolled as controls and 40 as cases.

All patients who fulfill the inclusion criteria were explained about the procedure. Patients who had spontaneous menstrual cycles on days 2 or 3 visited the OPD during the study duration; patients who had not performed a hormonal profile previously with an age between 20 to 40 years and who agreed to consent were included. First, verbal consent was sought, and later, written consent was obtained. The patients were informed about the procedure and the voluntary nature of their participation. After consent, the patient agreed to undergo transvaginal ultrasonography by the investigator himself using a transvaginal probe of a Samsung-Madison Ultrasound machine with a frequency of 6 MHz. Meanwhile, the patients who had endometrosis, ovarian surgery for ovarian cysts and tumors, chemotherapy and hormonal treatment, and polycystic ovary syndrome were excluded from the study.

The number of basal antral follicles measuring 2–10 mm in size was counted in each ovary. The sum of the counts of both ovaries was recorded separately. On the same day, a venous blood sample was withdrawn and sent to the hospital laboratory for tests of serum AMH and FSH and Thyroid function test. Serum, AMH, FSH, and Thyroid function test results and ultrasound findings of the AFC of the patients were recorded for further analysis. All patients included in the study were divided into 2 categories according to their TSH results: 1) <4.5 MIU/ml, 2) ≥4.5mIU/ml. Between all these groups, AFC, serum AMH, and FSH laboratory and demographic characteristics are compared. In addition, the correlation relationship between AMH, FSH, AFC, and TSH was analyzed.

The data was entered in Excel, and further analysis was performed in the SPSS-22 version. The ethical consent was obtained from the Institutions Review Board (IRB) and the National Academy of Medical Sciences (NAMS):84812079180

RESULTS FROM FINDING

Background of the study population

A total of 133 infertile women visiting PMWH hospital and who fulfilled the inclusion criteria were covered by the study. The study population was divided into case and control on the basis of the level of the TSH; control having TSH less than 4.5 mIU/ml (N=93) and case having TSH level 4.5 mIU/ml or more (N=40).

Three-fourths (75%) of the control were aged 26-40 years and the mean age of the participants was 29.5±6. On the other hand, 77.8% of the case were belonged to the age group of 26-40 with mean age of 29.1±5. Highest proportion of the individuals in both the control and case group belonged to Bagmati province 69% and 76% respectively followed by Gandaki province (10% and 13% respectively).

Table 1 Background of study population

%		Control (TSH<4.5)		Case (TSH≥4.5)		Total	
		N	%	N	%	N	
Age	≤25 years	23.7	22	22.5	9	23.3	31
	>25	76.4	71	77.5	31	76.7	102
	Mean±SD	29.5±6		29.1±5		29.4±5	
Province	India	1.1	1	0	0	0.8	1
	Koshi Province	3.2	3	5	2	3.8	5
	Madhesh Province	4.3	4	5	2	4.5	6
	Bagmati Province	68.8	64	77.5	31	71.4	95
	Gandaki Province	9.7	9	12.5	5	10.5	14
	Lumbini Province	5.4	5	0	0	3.8	5
	Karnali Province	3.2	3	0	0	2.3	3
	Sudurpaschim Province	4.3	4	0	0	3	4
Total		**100**	**93**	**100**	**40**	**100**	**133**

MEDICAL HISTORY OF THE PARTICIPANTS

More than half of the control (56%) and case (53%) weighted less than 60 kg. Majority of the surveyed participants were infertile since six years. All of the participants were included in the study in the early stage of the menstrual cycle**.** Regarding the AFC, a higher proportion of the control group (26%) had AFC's count above 10 in comparison to the case (13%). The majority of the participants had AFC of 5-10 in both control (67%) and case (70%). More than half (54%) had AMH level between 1-4 while the longer majority of the participants (81.2%) had FSH between 4-21. Almost all of the participants had FT3 levels between 2-5 (94%) and FT4 less than 1 (70%).

Table 2 Medical history of the participants

%		Control (TSH<4.5)		Case (TSH≥4.5)		Total	
		N	%	N	%	N	
Weight (Kg)	< 60	55.9	52	52.5	21	55	73
	≥60	44.1	41	47.5	19	45	60
Duration of infertility (Yrs)	≤6	65.6	61	72.5	29	68	90
	>6	34.4	32	27.5	11	32	43
Day of menstrual cycle	2	47.3	44	52.5	21	49	65
	3	52.7	49	47.5	19	51	68
Use of levothyroxine	Yes	8.6	8	42.5	17	19	25
	No	91.4	85	57.5	23	81	108
AFC	<5	7.5	7	17.5	7	11	14
	5-10	66.7	62	70	28	68	90
	>10	25.8	24	12.5	5	22	29

AMH (ng/ml)	< 1	7.5	7	7.5	3	7.5	10
	1-4	52.7	49	57.5	23	54	72
	>4	39.8	37	35	14	38	51
FSH (mIU/ML)	< 4	17.2	16	12.5	5	16	21
	4-21	79.6	74	85	34	81	108
	> 21	3.2	3	2.5	1	3	4
FT3 (pg/ml)	< 2	3.2	3			2.3	3
	2-5	91.4	85	100	40	94	125
	> 5	5.4	5			3.8	5
FT4 (ng/dl)	< 1	71	66	67.5	27	70	93
	1-2	22.6	21	17.5	7	21	28
	> 2	6.5	6	15	6	9	12
Total		**100**	**93**	**100**	**40**	**100**	**133**

Correlation between independent variable and TSH hormone

Pearson's correlation was used to analyze the correlation between the dependent variable ovary reserve function and independent variables TSH, thyroid hormone, age and weight. Correlation was observed between the AMH and FT4 in the case group (p=0.034, r=0.337), which indicated that AMH and FT4 are significantly correlated. The coefficient 'r' is positive (r=0.337) for the case suggesting that there is moderate positive linear relationship between the variables.

No other significant correlation between thyroid hormones and ovary reserve was seen. Negative correlation coefficient 'r' was observed in the table, which indicates that negative correlation between the variables. However, the value of r is close to zero in most of the cases which suggests that there is almost no linear relationship between the dependent and independent variables. Furthermore, the p-value of each crosstab is more than 0.05 thus, no statistically significant relationship has been established. There is no sufficient evidence to conclude that there is a significant correlation between the dependent and independent variables.

Table 3 Pearson's Correlation between independent variable and TSH hormone

		AMH (ng/ml)	FSH (mIU/ml)	AFC
Control (TSH <4.5)	TSH (mIU/ml)			
	r	0.061	-0.132	0.026
	p	0.564	0.206	0.804
	FT3 (pg/mL)			
	r	0.099	-0.027	0.01
	p	0.343	0.795	0.927
	FT4 (ng/dL)			
	r	-0.027	-0.034	-0.019
	p	0.796	0.748	0.855
	Age (Years)			
	r	-0.118	0.057	-0.47
	p	0.261	0.585	0.652
	Weight (Kg)			
	r	-0.008	-0.084	0.015
	p	0.94	0.426	0.888
Case (TSH≥4.5)	TSH (mIU/ml)			
	r	-0.011	-0.06	0.05
	p	0.949	0.713	0.759
	FT3 (pg/mL)			
	r	0.298	-0.2	0.149
	p	0.062	0.215	0.357
	FT4 (ng/dL)			
	r	0.337	-0.061	0.075
	p	0.034**	0.709	0.645
	Age (Years)			
	r	-0.168	0.134	-0.167
	p	0.301	0.409	0.302
	Weight (Kg)			
	r	0.206	0.244	0.103
	p	0.203	0.13	0.526

** Significant

Spearman's correlation (Test of monotonic relationship)

Further Spearman's correlation was used to investigate the non-linear or monotonic relationship between the dependent and independent variables.

In the control group, AMH and FT3 (p=0.027, r=0.229) were found to have statistically significant correlation between the variables being analyzed. The positive coefficient indicates the non-linear directly proportional relationship between the variables. Similar to Pearson's correlation test, the negative value of the coefficient represents the inverse relationship and its value closer to zero indicates insignificant relationship. The p-value of most of the dependent and independent variables are more than 0.05, which demonstrates no significant relationship between the study variables.

Table 4 Spearman's Correlation between independent variable and TSH hormone

		AMH (ng/ml)	FSH (mIU/ML)	AFC
Control (TSH <4.5)	TSH (MIU/ML)			
	r	0.028	0.041	-0.034
	p	0.791	0.695	0.746
	FT3 (pg/mL)			
	r	0.229	0.084	0.096
	p	0.027**	0.423	0.362
	FT4 (ng/dL)			
	r	-0.018	0.022	0.047
	p	0.861	0.833	0.657
	Age			
	r	0.073	-0.121	-0.01
	p	0.489	0.248	0.923
	Weight			
	r	0.105	-0.152	-0.002
	p	0.519	0.145	0.986
Case (TSH≥4.5)	TSH (mIU/ML)			
	r	0.15	0.017	0.21
	p	0.328	0.919	0.192
	FT3 (pg/mL)			
	r	0.17	-0.226	-0.24
	p	0.293	0.16	0.136
	FT4 (ng/dL)			
	r	-0.171	0.051	-0.24
	p	0.293	0.754	0.136
	Age			
	r	-0.175	0.209	-0.139
	p	0.28	0.195	0.393
	Weight			
	r	0.105	0.17	0.76
	p	0.519	0.293	0.642

** Significant

DISCUSSION

Thyroid hormones are responsible for the normal development and works to function on different organs.[10,11] TSH, FT3, and FT4 can bind to receptors on ovarian cells and participate in the regulation of ovarian function.[12] In this study, TSH was grouped into TSH<4.5 mIU/L and ≥4.5 mIU/L. The results showed that there was a significant correlation between AMH and FT4, AMH and FT3. This result suggests that there may be clear correlation between thyroid hormone levels and ovarian reserve in women with infertility. Subclinical hypothyroidism (SH) is defined as having abnormally high TSH levels with normal free thyroxine levels, and no overt hypothyroidism symptoms. It is a frequent condition in the general population, and it is reported to be more prevalent in infertile women, where it is reported to be 13.9%, compared to 3.9% in healthy fertility-proven women.[13] In women who are experiencing infertility problems, the association between TSH and AMH levels seems to be unclear. Age, Body Mass Index (BMI), and underlying diseases like Polycystic Ovarian Syndrome (PCOS) are some of the factors which influence the relationship between TSH and AMH in infertility.[14] It is important to take into account that the link has not consistently been demonstrated in every study.

There is a positive correlation between AMH and TSH level in our study. It is probably due to most of the cases

were SH and also small number of sample size. Similar study done by Demirci and Apaydin in 2020 showed that there was no correlation found between AMH level in subclinical hypothyroid and euthyroid patient groups.[15] However, in a study conducted by Soam et.al in 2022 revealed that serum AMH levels and TSH levels had a negative relationship. A greater serum TSH levels were seen in the infertile females with low AMH values compared to the fertile females, demonstrating a direct relationship between greater serum TSH levels and female fertility.[16] Another study conducted by Kuroda et al in 2014 showed TSH and AMH levels in infertile women revealed an inverse association. TSH may influence ovarian reserve in people who are infertile, according to a further explanation. Additionally, women with subclinical hypothyroidism have a higher chance of experiencing infertility, and high TSH levels can affect ovarian function.[17] The interpretation of TSH and AMH values in the context of infertility requires individualized assessment and consultation with a healthcare practitioner.[18]

In a 2019 study, Rao et al. found a significant association between isolated SH and a decreased AFC (p=0.005). The findings of this research further suggest that SH is linked to a reduced ovarian reserve in older women of reproductive age (≥35 years)[19]. However, there were no correlation between TSH and FSH in our studies. The limited correlation in our study could be due to the limited number of studies enrolled in our research. Therefore, further research is warranted to explore the underlying mechanisms behind these relationships and their clinical implications. This knowledge can potentially assist healthcare professionals in developing more tailored and effective treatment approaches for infertile women based on their ovarian reserve and thyroid hormone profiles.

The ovarian reserve and thyroid function test in infertile women were not significantly correlated, according to this study. The following are some limitation on this study. There is a small sample size and most people have milder elevations in their TSH levels; more research is needed to determine the association between the duration of poor thyroid function and ovarian reserve. In addition, the variables such as the patient's age, BMI, and lifestyle factors should be considered in the forthcoming studies along the clinical factors. Future research is therefore needed to learn more about the molecular processes that control the decreased ovarian reserve in thyroid disordered women.

CONCLUSION:

In conclusion, this study aimed to investigate the relationship between ovarian reserve test and thyroid hormone level in women with infertility. Two groups were divided on the basis of the TSH level, control (TSH<4.5) and case (TSH≥4.5). Based on the findings of the study of Pearson's correlation test, AMH and FT4 were found to be statistically significant and have moderate positive relationships for the case group, which suggests that, with increase in level of AMH, FT4 also tends to increase. In addition, Spearman's correlation test was used to further explore the non-linear relationship, which helped to establish the positive significant correlation in the control group between AMH and FT3. Thus, we can conclude that thyroid hormones have a positive relationship with the ovarian reserve in the infertile women. That is, with a decrease in thyroid hormones, there is a decrease in ovarian reserve.

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Functional Outcome of Micro Lumbar Discectomy in Patients with Symptomatic Lumbar Disc Herniation

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ABSTRACT

INTRODUCTION: Lumbar disc herniation is a common cause of back and leg pain. Though the majority of symptomatic lumbar discs can be conservatively treated, surgical decompression is indicated in a subset of patients. Micro lumbar discectomy provides excellent results in the short-term period with relief of leg pain and early return to work

METHOD: This is a Retrospective study of 70 patients who underwent micro lumbar discectomy for symptomatic lumbar disc herniation with leg pain, straight leg raising test positive, MRI evidence of disc herniation, and failed conservative treatment of minimum 2 months duration. Patients with cauda equina, profound neurological deficits, multiple disc herniation, and previous lumbar spine surgery were excluded. All patients were surgically managed at National Trauma Centre, Kathmandu, Nepal, and had a minimum follow-up of 2 years

RESULT: A total of 70 patients were treated with Micro lumbar discectomy Out of these, 40 (57.1%) cases were male, and 30 (42.9%) were female. The commonest level involved was l4/l5 (35%) followed by (14%) l5/S1

CONCLUSION: Functional outcome of micro lumbar discectomy produces excellent results and is still a standard surgical technique for symptomatic lumbar disc herniation with minimum resources and low postoperative complications

KEY WORDS: *Back pain, Lumber spine, Micro lumber discectomy*

INTRODUCTION

Lumbar disc herniation (LDH) is a common cause of back and leg pain. Symptomatic lumbar disc herniation is herniated disc in the spine is a condition during which a nucleus pulposus is displaced from intervertebral space causing back pain and neurological features like radiation, and claudication.[1] It occurs due to the degeneration of the intervertebral disc with subsequent prolapse of the nucleus pulposus through a defect in the annulus fibrous. Lumbar disc herniation occurs in 35% of men and 45% of women.[2] It also forms the second most common cause for medically authorized absence from work, The first lumbar disc surgery was done by Dandy in 1929.[3] Since then various operative procedures have been performed in disc surgery. Conservative treatment gives satisfactory results with disc herniation in the few months of treatment onset. This is likely to occur particularly in patients with mild or moderate nerve root compression. Surgical treatments give significantly faster and more satisfactory results. Some surgical complications were noted and chances of recurrences of radicular and low back pain Herniated lumbar disc is a displacement of the disc material. A herniated intervertebral disc is a disease that is the main cause of sciatica and severe low back pain

Conservative treatment with medicine, physiotherapy, epidural injection, and selective nerve root block

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are the modalities of treatment. Failure to which or severity of disease ends up with surgical management. There are two modalities of surgical management for disc herniation one is conventional and other one is a microdiscectomy.[4]

Conventional disc herniation surgery has a large incision size, as well as the bulk of tissue injury with prolonged surgical time, might have complications like severe pain, high rate of surgical site infection as well as a high rate of Dural tear and nerve injury. Micro lumbar discectomy, the small incision as well less soft tissue injury with lesser surgical time seems to have better post-operative pain relief as well as Minimal operative soft tissue injuries and infections, fewer hospital stays and early return to daily work.[5]

Thus the rationale of this study is to see the outcomes of micro disc herniation which might result in a change in the practice of the spine surgeon if the outcome will be similar to the other studies done in other parts of the world. Furthermore, This technique might help surgeons for better patient management for post-operative pain and other functional outcomes as well as infections.

METHOD

A prospective observational study was conducted on patients with lumbar disc herniation presented at the national trauma center over a period of two years. A total of 70 cases participated in the study using the census method. Approval of the study was taken from the Institutional Review Board NAMS, Bir Hospital.

Quantitative data will be expressed as mean and standard deviation, whereas categorical variables will be presented as numbers and percentages. Quantitative data will be analyzed using an independent *t-test*. The chi-square test will be used to compare the sex preoperative and postoperative motor and sensory, Duration of motor and sensory. A P value>0.05 will be considered statistically significant.

After approval of IRB. Patient attending OPD who has symptoms of disc herniation like back pain claudication as well as leg pain and numbness and tingling sensation as well as failed conservative management patient counsel for disc herniation surgery by any spine surgeon of the unit. Once the confirmation of surgery is done based on the discretion of the operating surgeon either micro or conventional lumbar discectomy will be planned. Researchers will counsel those patients who are planning for microdiscectomy patients for observation research, after the consent from the patient researcher will do observations. Surgery will be done by a senior consultant spine surgeon.

Observation will be done for the patient who has symptomatic lumbar disc herniation requiring surgical intervention attending in trauma OPD. The following symptoms are observed preoperatively, and patient demographic profiles like age sex, Duration of illness as well as preoperative sensory and motor function will be assessed via MRC (Medical Research Council) Muscle Power grading. After completion of all the preoperative investigations and radiological images, the patient planned for surgery. As per institutional protocol, most of the patients are going for micro lumbar discectomy in our center. After general anesthesia, the position of the patients will be prone, and using the posterior midline approach opening the ligamentum flavum, hemilaminectomy, foraminotomy, and microdiscectomy will be performed. Nerve root release and herniated disc resection will be done. The aponeurosis, subcutaneous fascia, and skin will be closed. In these studies, Data will be collected by surgeons. In the post-operative ward pain assessment will be done by VAS scale and categorized into no pain, mild, moderate, and severe pain then the number of patients in each group will be recorded. The neurological function of the patient will be assessed via ASIA chart in the post-operative ward once the effect of the anesthesia is over. During the hospital stay, patients will be assessed and recorded if signs of infection will be found. Patients will be kept in follow-up weekly for a 6-month period and work performance as well as ease will be documented based on the Macnab criteria.

Macnab Criteria[13]

Excellent(1)	No pain no restriction of mobility, returns to work original level of activity
Good (2)	Occasional nonradicular pain, return to modified work
Fair(3)	Some improved functional capacity, still handicapped unemployed
Poor(4)	Continued objective symptoms of root involvement, additional operative intervention needed at the index level

RESULT

A total of 70 patients were treated with Micro lumbar discectomy Out of these, 40 (57.1%) cases were male, and 30 (42.9%) were female. Age in years (Mean + SD) Min-Max 40.06% +11.22%(20-64) of the patient was around 40 ranged from 20 to 64 years. as in Figure 1

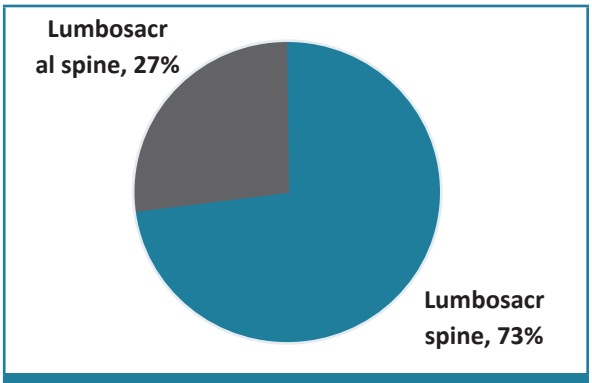

Figure 2. Level of Spine

The majority of the cases were lumbar spine 73% followed by lumbosacral spine 27% as shown in Figure 2.

Table 2: Neurology of cases

Neurology	Number	Percentage
Intact	31	44.28
Left leg pain	8	11.4
Right leg pain	10	14.28
Left leg Radiculopathy	4	5.71
Right leg Radiculopathy	6	8.57
Others	12	17.14

Table 3: Diagnosis of cases

Diagnosis	Frequency (n)	Percentage (%)
L4L5 PIVD with Rt L5 root compression	1	1.43
L4L5 stenosis with left leg radiculopathy	1	1.43
L5S1 PIVD Right Paracentral	1	1.43
Left L4L5 PIVD with Rt foot drop	1	1.43
Left L5S1 PIVD with sequestration	1	1.43
Left L5S1 sequestrated and inferiorly migrated disc	1	1.43
Lt L4L5 PIVD and NF stenosis	1	1.43
Lt paracentral PIVD	24	34.29
Lt stenosis with left leg radiculopathy	5	7.14
PIVD L4L5 with Rt L5 radiculopathy	1	1.43
PIVD L4L5 with Left L5 radiculopathy	1	1.43
Recurrent Right L5S1 PIVD	1	1.43
Right L3L4 PIVD with Rt L4 root compression	1	1.43
Rt L4L5 inferiorly migrated disc with Rt L5 root compression	1	1.43
Rt L4L5 PIVD with Rt L5 root compression	1	1.43
Rt Paracentral PIVD	22	31.43
Rt Stenosis with Rt. leg radiculopathy	6	8.57

About two third of the cases were diagnosed with paracentral PIVD of total cases. Stenosis with leg radiculopathy was found in 11 (16% cases).

Table 4: Surgery performed

Surgery name	Right	Left
L4L5 MLD	4	17
L5S1 MLD	19	9

Table 5: The mean difference of VAS score Pre-Operative and Post Operatively

	Time Duration	N	Mean Differences	SD	P-value
VAS for pain	Preoperatively	70	8.76	0.88	
	1 week postoperatively	70	4.76	0.44	<0.001
	3 months postoperatively	70	1.85	0.43	<0.001
	6 months postoperatively	70	0.89	0.24	<0.001
	One year postoperatively	70	0.50	0.22	<0.01
	Two years postoperatively	65	0.40	0.36	<0.01

We performed a paired T-test to see if the postoperative pain is reduced significantly as in Table 5. The post-operative VAS score is reduced significantly after one-year follow-up.

Table 6: Modified Macnab criteria for the assessment of clinical outcomes after Microlumbar Discectomy.	
Outcome	No (%)
Excellent	41(58.57)
Good	26 (37.14)
Fair	3 (4.28)
Poor	0
Total	70

As per table 6. About 60 percent of total cases had excellent outcome followed by good as per Macnab criteria. There were no single cases of poor outcome.

DISCUSSION

The aim of this study was to analyze the Functional outcome of patients undergoing micro disc herniation surgery for symptomatic lumbar disc herniation over the study period.

In our study, a total of 70 patients were treated with Micro lumbar discectomy out of these, 40 (57.1%) cases were male, and 30 (42.9%) were female. Age in years (Mean + SD) Min-Max 40.06% +11.22% (20-64) of patients was around 40 ranging from 20 to 64 years. Our study was similar to the study done by Bartlomiej K[6] where there were 149 male and 137 Female patients. In another study which is close to our study done by Yadav RM[10] the total number of 31 patients. Out of 31 patients, 19 were male and 12 were female with a mean age of 35 years.

our study showed the most commonly involved level was l4/l5 vertebrae and followed by L 5/S1 Which was similar to the study done by Kaushal P[7] et al which was a prospective study of 220 cases in a period of 8 years in patients who underwent mini discectomy. In their study they found that the commonest level involved was L4/L5 followed by L5/S1 vertebrae which was comparable to our study.

In our study, the VAS score is 90%. A similar study was done by Sedighi [11] They evaluated 148 patients who had an operation for lumbar disc herniation. In their study, they concluded that the VAS score was 93.3%.

In our study, according to Modified, Macnab's Criteria were excellent in 41 cases, good in 26, and fair in 3 cases. The study which was close to our study done by Yadav RM[10].They concluded that the final follow-up Modified Macnab's Criteria was excellent in 13 cases, good in 16, and fair in 2 cases. Their study concluded that removal of the herniated disc to decompress the nerve root provides rapid relief of symptoms and improved quality of life and early return to work.

CONCLUSSION

Functional outcome of micro lumbar discectomy produces excellent results and still a standard surgical technique for symptomatic lumbar disc herniation with minimum resources and low postoperative complications

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Association of Lower Urinary Tract Symptoms with Body Mass Index in Women Attending Gynecology Clinic in a Tertiary Care Center in Nepal

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ABSTRACT

INTRODUCTION: Lower urinary tract symptoms (LUTS) is a very prevalent condition worldwide, including Nepal. Among several risk factors, body mass index (BMI) has also been attributed to its development. We intended to see if a high BMI is associated with LUTS in our population.

METHOD: An observational analytical study was conducted among 246 women who attended the gynaecologic clinic of a tertiary care center in Kathmandu, Nepal. Sociodemographic, anthropometric, clinical, gynecological and characteristics pertaining to LUTS were recorded. Descriptive statistics were used to describe the study sample. A binary logistic regression analysis was performed to find the association of BMI with LUTS.

RESULT: The incidence of LUTS was 43.5%. Frequency (22.3%) was the most common subtype followed by urgency (20.14%) and nocturia (17.9%). Obese patients (BMI > 30 kg/m^2) had 1.72 (1.12-2.65; p= 0.01) times the probability of having LUTS than those with a normal or low BMI (BMI <25kg/m^2).

CONCLUSION: LUTS was very common in women presenting to the gynecological clinic in our tertiary care center. Frequency was the commonest symptom. High BMI was found to be strongly associated with presence of LUTS.

KEY WORDS: *body mass index, lower urinary tract symptoms, women*

INTRODUCTION

Lower urinary tract symptoms (LUTS) in women is a common condition with worldwide prevalence.[1-2] The prevalence, however, varies widely as it depends on age, geography and culture, and is particularly high in ages above 40 with reports as high as 76%.[3] LUTS as per International Continence Society (ICS), consists of storage, voiding and post-micturition symptoms. The storage symptoms include overactive bladder (OAB) and urinary incontinence (UI); the voiding symptoms include slow or weak stream, hesitancy and terminal dribble; and post-micturition symptoms consists of incomplete emptying and post-micturition dribble.[4-6]

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Several risk factors have been reported to be associated with LUTS including increasing age, pregnancy, childbirth, diabetes and smoking. Previous major pelvic surgery and hereditary factors can also influence the development of LUTS.6 Some studies have shown tendencies in females with high body mass index (BMI) for developing LUTS. This has even attributed to excess weight in the abdominal area which increases the abdominal pressure and as a consequence increases the pressure of the bladder and causes mobility of the urethra.7-8 Another explanation is that release of cytokines by adipose tissue can promote the urgency to urinate and thereby contribute to mixed type of UI.9

As per our knowledge, there are no published data regarding the prevalence of LUTS in our population, neither there is any data depicting its association of BMI with LUTS. This study was performed to find the association of LUTS with BMI in our setting. The assessment of risk factors, particularly BMI, could allow simple interventions like life-style changes such as diet and exercise to help reduce LUTS. Furthermore,

a detailed knowledge of the natural history of LUTS in women with determination of various types of LUTS in our population could help improve and streamline urogynaecological services in Nepal.

METHOD

This was an observational analytical study conducted in Paroparkar Maternity Hospital, Kathmandu, Nepal, a tertiary care government hospital dedicated to the care of women. Women over the age of 18 years who attended the gynecology clinic were included in the study. Women, who did not give informed consent for the study, pregnant women and postpartum women were excluded from the study.

A convenience sampling technique was used to enroll patients. With an expected prevalence of 20% (P),10 and allowing a confidence interval of 95% (z) and error of margin of 5% (d), a sample size of 246 patients was calculated using the formula $n= Z^2 P(1-P) / d^2$.

After approval from the Institutional Review Board,National Academy of Medical Sciences, data was collected using a proforma. Sociodemographic data, menstrual history, obstetric history, personal history, medical comorbidities and past pelvic surgeries were recorded. Anthropometric measurement, which included height and weight, were taken and BMI calculated accordingly. Presence of LUTS and its different subtypes (urgency, nocturia, urinary incontinence, stress incontinence, urge incontinence, interruption, dysuria, hesitancy, frequency, and bladder pain syndrome) as well as their severity were determined using a validated questionnaire (International Consultation on Incontinence Modular Questionnaire for Female Lower Urinary Tract Symptoms- ICIQ-FLUTS11) translated by a certified translator into Nepali and reviewed by two urogynecologist for content validity.

After checking for correctness and completeness, the information was entered into Microsoft Excel Program. Statistical Package for the Social Sciences (SPSS) version 16 was used for analysis. Categorical data were presented as percentage, whereas numerical data were described in terms of mean and standard deviation for normal distribution, or median and interquartile range for skewed distribution. Categorical variables were compared using Chi-square analysis, T-test was applied for parametric variables and Mann-Whitney U test was performed to compare non-parametric variables. Binary logistic regression was used to determine the association of BMI with development of LUTS. A p-value of less than or equal to 0.05 was considered significant.

RESULTS

Patients were recruited from October 2022 to March 2023. The incidence of LUTS in the study was 43.5%. The mean age, height and weight of the population were 45.29, 1.525m, 61.05 kg, whereas the median BMI was 26.2 kg/m2. According to BMI category, 39.4% had BMI less than 25, 49.1% were overweight (BMI of 25-30) and 11.5% were obese (BMI > 30).

Table 1. Characteristics of patients in those with and without LUTS

	LUTS negative	LUTS positive	p-value
Age (mean, SD)	43.59 (11.58)	46.99 (11.93)	0.03
Height, m (mean, SD)	1.53 (0.08)	1.52 (0.07)	0.50
Weight, kg (mean, SD)	60.55 (8.20)	61.56 (9.56)	0.39
BMI (median, IQR)	25.66 (23.44-28.10)	26.89(24.55-28.93)	0.04
BMI category (N, %)			0.03
<25	51(47.6)	46 (33)	-
25-30	50 (46.7)	71 (51)	-
>30	6 (5.7)	22 (16)	-
Alcohol consumer (N, %)	9 (8.4)	27 (19.4)	0.03
Smoking (N, %)	21 (19.6)	46 (33.1)	0.04
HRT (N, %)	2 (1.8)	4 (2.8)	1.00
Menopause (N, %)	35 (32)	72 (51.17)	0.01
Mode of delivery (N,%)			0.57
None	3 (2.8)	2 (1.4)	-
Vaginal	76 (71)	115 (82.7)	-
Cesarean section	18 (16.8)	22 (15.8)	-
Comorbidities (N, %)			<0.001
None	94 (87.8)	91 (65.5)	-
Diabetes mellitus	1 (0.9)	24 (17.2)	-
Hypertension	4 (3.7)	20 (14.3)	-
Others	1 (0.9)	6 (4.3)	-
Previous pelvic surgery (N, %)	23 (21.4)	32 (23)	1.00

LUTS: lower urinary tract symptoms; HRT: hormone replacement therapy; N: number; SD: standard deviation; IQR: interquartile range

Table 1 summarizes the characteristics of the study participants according to the presence of LUTS. The BMI was found to be lower in patients without LUTS compared to those with LUTS (median (IQR) 25.66 kg/m2 (23.44-28.10) vs 26.89 kg/m2 (24.55-28.93)). Mean age, alcohol consumption, smoking, menopause status, and presence of comorbid conditions were also significantly lower in those without LUTS than in those with LUTS. Similarly, according to BMI category, a higher proportion of overweight (51% vs 46.7%) and obese patients (16% vs 5.7%) were found in the LUTS group.

Figure 1 describes the incidence of various types of LUTS as well as their severity scale as determined from the questionnaire. Frequency (22.3%) was the most common symptom, followed by urgency (20.14%) and nocturia (17.9%). Stress urinary incontinence (15.8%), dysuria (16.5%) and bladder pain (14.4%) were also common symptoms. Urinary incontinence (5%), hesitancy (4%), and interruption (2%) were the least common symptoms.

Binary logistic regression analysis was performed to assess the association of BMI with the presence of LUTS (Table 2).

Table 2. Binary logistic regression analysis

Variable	Odds ratio	95% C.I		p-value
		Lower	Upper	
Age	0.99	0.96	1.028	0.71
BMI	1.72	1.12	2.65	0.01
HRT	1.15	0.19	6.93	0.87
Menopause	2.03	0.92	4.51	0.08
Smoking	1.12	0.54	2.32	0.76
Alcohol	2.10	0.84	5.25	0.11
Mode of delivery	1.01	0.47	2.18	0.98
Previous pelvic surgery	1.17	0.54	2.56	0.68

BMI: body mass index; HRT: hormone replacement therapy; C.I.: confidence interval

For all subtypes except frequency and nocturia, 0- never, 1- occasionally, 2- sometimes, 3-most of the times, 4- all of the time. For nocturia, 0- none, 1- one time, 2- two times, 3- three times, 4- four or more times. For frequency, 0- 1 to 6 times, 1- 7 to 8 times, 2- 9 to 10 times, 3- 11 to 12 times, 4- 13 or more times.

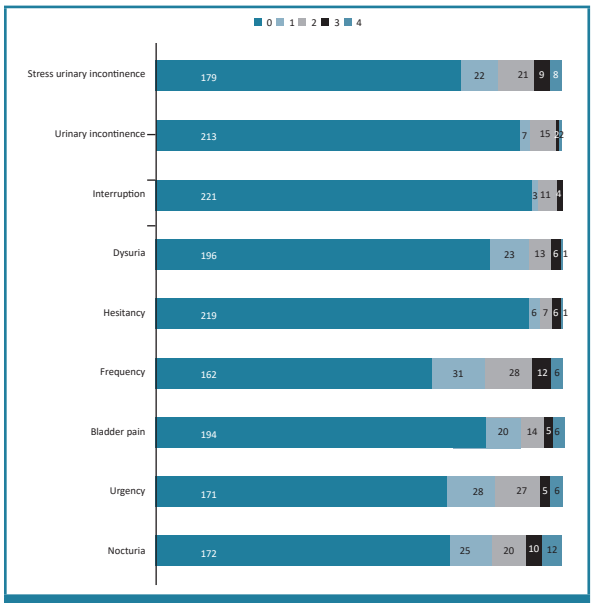

Figure 1. Types and severity of LUTS

DISCUSSION

In this study conducted in women attending gynecology clinic in a tertiary care center in Nepal, increasing BMI was associated with presence of LUTS. The association was observed when the presence of LUTS was compared with median BMI as well as BMI classified according to severity. This association was further established by using binary logistic regression, where variables, decided pre-hoc, were tested for confounding. Obese patients (BMI > 30 kg/m2) had an odds of 1.72 (1.12-2.65; p-value 0.01) in having LUTS compared to those with a normal or low BMI (BMI <25kg/m2).

These results are consistent with many previous studies from around the world. A study from the United States reported that women with a BMI > 30kg/m2 had an odds of 1.77 in having urinary incontinence compared to women with a BMI < 30 kg/m2, which is quite comparable to our results.12 Another study from Denmark found that obese women were more than twice as likely to have urinary incontinence than underweight women.13 A study done in Mexico observed that women with urinary incontinence had a higher BMI than those who were continent (24.6+/-4 vs 27+/-5.5 kg/m2, p<0.0001).14 Elia G et al. after adjusting for prior bladder surgery, any surgery, history of medical problems and physical inactivity, only the association between BMI and incontinence remained statistically significant (adjusted OR 1.95; 95% CI 1.18-3.19).15 A retrospective study by Santaniello F et al.

found that incidence of urinary incontinence rose as the BMI increased, with 70.8% complaining of urinary symptoms in class I BMI, increasing to 78.9% in class II, 95.1% in class III and all 16 patients in BMI class IV were incontinent.[16]

Most of these studies have only reported the association of urinary incontinence with BMI. However, our study encompasses all the spectrum of LUTS and shows that there is an overall association of BMI with LUTS. This finding is corroborated by a large observational cross-sectional study which found a correlation between the presence of urinary urgency (r=0.7; P=0.00), nocturia (r=0.7; P=0.00), and urinary incontinence (r=0.9; P=0.00) with waist circumference, which is a parameter closely related to BMI.[17]

The biological plausibility for the association between BMI and LUTS has been explained by the fact that individuals who are overweight have undue pressure placed on the bladder and surrounding muscles.[18,19] Being overweight, especially with central adiposity, increases intra-abdominal pressure and, thus, pressure on the bladder and pelvic organ support structures. As this abdominal pressure upon the bladder increases, the severity of LUTS also increases.[20]

Almost half of the patients (43.5%) had some or other form of LUTS of various severity indicating that it is a very common condition in our population. Studies from other population settings have also reported similar incidences with one from Malaysia showing 50.6%.[21]

The commonest symptom of LUTS in our study was frequency. This is in contrast to most studies, where stress urinary incontinence is the more common feature. One study observed that 49% of the symptoms were due to SUI.[21] However, in a study done by Pradhan T et al. in Nepal 13, 82.4% patients had complaints of overactive bladder symptoms such as urgency, urge incontinence and increased daytime frequency.[22]

The limitation of this study was that it was a single center study. Nevertheless, the setting where it took place was a high-volume center with good representation from almost all areas of Nepal. This study focused only on association of incidence of LUTS and not its implications such as quality of life.

CONCLUSION

LUTS was very common in women presenting to the gynecological clinic in our tertiary care high volume center. Frequency was the commonest symptom and most symptoms were of mild severity. High BMI was found to be strongly associated with presence of LUTS.

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Evaluation of P16 in Oral Cavity and Oropharyngeal Carcinoma

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ABSTRACT

INTRODUCTION: Oral cavity and oropharyngeal carcinoma is the sixth most common cancer worldwide, and squamous cell carcinoma is the most prevalent. The etiological factors are smoking, tobacco chewing, alcohol consumption, poor oral hygiene and human papilloma virus (HPV) infection. HPV infects basal epithelial cells through abrasion or minor trauma. Tumorigenesis is caused by HPV E6 and E7 proteins which decrease levels of p53 and Rb tumor suppressor proteins leading to aberrant overexpression of cell cycle protein p16.

METHOD: This is a prospective, correlational cross-sectional study carried out on 46 cases of oral cavity and oropharyngeal carcinoma during the period of June 2021 to May 2022, at the Department of Pathology, Bir hospital and National Path Labs, Maharajgunj. The surgical biopsy cases were subjected to H&E staining and P16 immunohistochemistry.

RESULT: Total 46 cases of oral cavity and oropharyngeal carcinoma were enrolled in this study. The most common carcinoma was squamous cell carcinoma with a common age group between 41 to 60 years of age showing male predominance. Tongue was the most common site. Out of 46 cases, 34 cases were P16 positive and 12 were P16 negative. The correlation between the P16 immunohistochemistry and squamous cell carcinoma of oral cavity and oropharynx was significant ($p<0.005$).

CONCLUSION: There is a good correlation between P16 immunohistochemistry and squamous cell carcinoma of oral cavity and oropharynx and hence P16 can be used as a surrogate marker.

KEY WORDS: *Immunohistochemistry, Oral cavity and oropharyngeal tumours, P16. Squamous cell carcinoma*

INTRODUCTION

According to the GLOBOCAN (Global Cancer Incidence, Mortality and Prevalence) 2018, more than 800,000 new Head and Neck Squamous Cell Carcinoma cases are diagnosed annually worldwide comprising the sixth most common cancer leading to more than 400,000 deaths annually. Prevalence of oropharyngeal carcinoma in the world is 3.68 and in Nepal is 1.81 and of the oral cavity is 11.97 in the world and 8.23 in Nepal.[1]

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More than 90% of oral cavity and oropharyngeal carcinomas are squamous cell carcinoma.[2] The different etiological factors of oral and oropharyngeal squamous cell carcinoma are tobacco chewing, smoking, alcohol consumption, poor oral hygiene and Human papilloma virus. Human papillomavirus (HPV) is a small, non-enveloped DNA virus belonging to the Papillomaviridae family.[3]

HPV infects the basal epithelial cells through wounds and abrasions. The viral DNA then gets integrated into the host genome. Tumorigenesis is caused by HPV E6 and E7 proteins which decrease levels of p53 and Rb tumor suppressor proteins leading to aberrant overexpression of cell cycle protein p16.[3]squamous cell carcinoma is the most frequent malignancy in oral cavity and 1 of the 10 most common cancers

worldwide. According to the most recent GLOBOCAN estimate in Europe between 2012 and 2015, there was an overall increasing incidence and mortality for oral cancer, mostly HPV-related in the oropharyngeal region with evidence of significant differences from the prognostic and therapeutic point of view. Areas covered: Until now, the management of the patients is based on classical histologic parameters such as TNM and tumor grading, but new molecular and cell markers have been investigated to improve patients' treatment and survival. Therefore, there is a need for new biomarkers characterizing the cancer diversity, with the consequent possibility of patient stratification for specific treatment. Expert commentary: This review aims to discuss some of the most relevant and novel genetic, epigenetic, and histological prognostic biomarkers in oral cancer, highlighting the main differences between HPV-unrelated oral squamous cell carcinoma (OSCC P16 is a surrogate marker for the detection of HPV infection.[4]

As the etiology of HPV positive and negative oral and oropharyngeal carcinoma is different, their treatment and prognosis also differ. HPV-related cancer has a good prognosis compared to non-HPV cases. So preventive measures in the form of HPV vaccination, targeted therapies against viral protein, and good response to treatment by HPV-positive cancers have made the need for pretreatment diagnosis of HPV-associated cancer and p16, a surrogate marker for the diagnosis.

Since oral and oropharyngeal carcinoma is in increasing trend due to human papilloma virus and there has been less research in our country, this study tends to correlate p16 immunohistochemistry with oral cavity and oropharyngeal carcinoma.

METHOD

This was a prospective, cross-sectional study conducted in the department of Pathology, National Academy of Medical Sciences, Bir Hospital, Kathmandu, from June 2021 to May 2022. Ethical approval was obtained from Institutional Review Committee of National Academy of Medical Sciences. Patients who have histopathologically proven oral cavity and oropharyngeal carcinoma and who gave consent to take part in the study were enrolled in the study. Patients who refused for study, benign lesion of oral cavity and oropharynx, inadequate biopsy, autolysed specimen, patients who have undergone chemotherapy or radiotherapy before surgery/biopsy were excluded from the study. A total of 46 cases fulfilling the criteria were included in the study.

The surgical biopsies from the oral cavity and oropharynx were collected in formalin and subjected to routine tissue processing and rotary microtome to prepare sections from paraffin blocks. Staining with H & E was done according to the guidelines given in the Bancroft's Theory and Practice of Histological Techniques 7th edition.

Histopathological diagnosis was established first by morphology on the H&E stained slide and the tissue block was taken to National Path Lab, Maharajgunj road, Kathmandu to perform immunohistochemistry staining for p16. The H&E slides were reported by multiple pathologists. The IHC stained slides were analyzed for p16 immunoreactivity and staining intensity. A known p16 expressing cervical SCC case was used as the positive control and sections of normal tonsil used for negative controls with each run.

RESULTS

During the study period between June 2021 to May 2022, a total of 4132 biopsy specimen were received in the Department of Pathology, Bir hospital, Mahaboudha, Kathmandu out of which 46 were carcinoma of oral cavity and oropharynx and were included in our study.

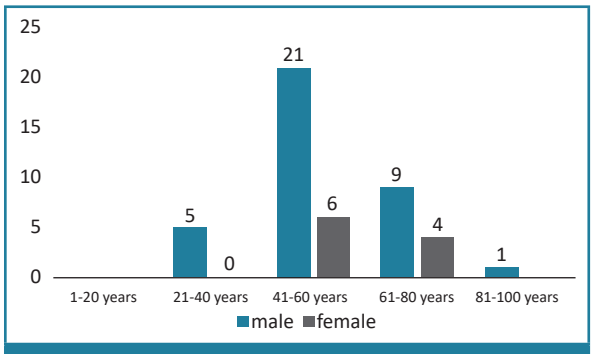

Chart 1. Incidence of Oral cavity and Oropharyngeal carcinoma with regard to age and sex.

Incidence of various oral cavity and oropharyngeal carcinoma in the present study is shown in Chart 1. Out of the 46 cases of oral cavity and oropharyngeal carcinoma, squamous cell carcinoma was the most common carcinoma constituting 97.80% (45/46) followed by adenocarcinoma (2.20%).

Table 1: Correlation of p16 immunoreactivity with subset of location of tumor

Site	P16 immunoreactivity		Total
	Positive	Negative	
Lip	1 (2.8%)	0	1
Tongue	14 (40%)	5	19
Gingivo buccal sulcus	2 (5.7%)	1	3
Buccal mucosa	5 (14.3%)	0	5
Tonsil	2 (4.3%)	0	2
Floor of mouth	4 (11.4%)	0	4
Base of the tongue	4 (11.4%)	2	6
Palate	2 (4.3%)	2	4
Retromolar trigone	1 (2.8%)	1	2
Total	35 (76.1%)	11 (23.9%)	46 (100%)

Table 1 demonstrates the correlation of different location of tumor with p16 immunoreactivity. This shows most common location of the tumor to be tongue i.e. 18 (39.1%) of the patient with maximum positivity. Lip, buccal mucosa, tonsil, floor of mouth and maxilla had 100% p16 immunoreactivity.

Table 2: Frequency of p16 intensity.

P16 immunoreactivity	P16 intensity	Frequency	Percent
Negative	0	11	23.9
Positive	1+	7	15.2
	2+	15	32.6
	3+	13	28.3
Total		46	100

Table 2 shows 23.9% of the tumors were found to be negative immunoreactivity to P16 in which intensity score was"0". Whereas 15.2% of the tumor showed intensity score of 1+, 32.6% showed intensity score of 2+ and 28.3% of tumors showed maximum intensity score of 3+.

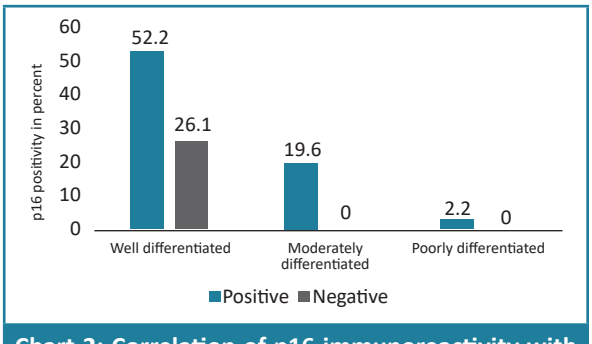

Chart 2: Correlation of p16 immunoreactivity with grading of the tumor.

Chart 2 demonstrates the correlation between tumor grades and p16 immunoreactivity. Well differentiated carcinoma constitute 78.3% in which 52.2 % are p16 positive and 26.1 % are negative while 19.6 % are moderately differentiated and 2.2 % are poorly differentiated both of which are 100% positive for p16.

PHOTOMICROGRAPHS

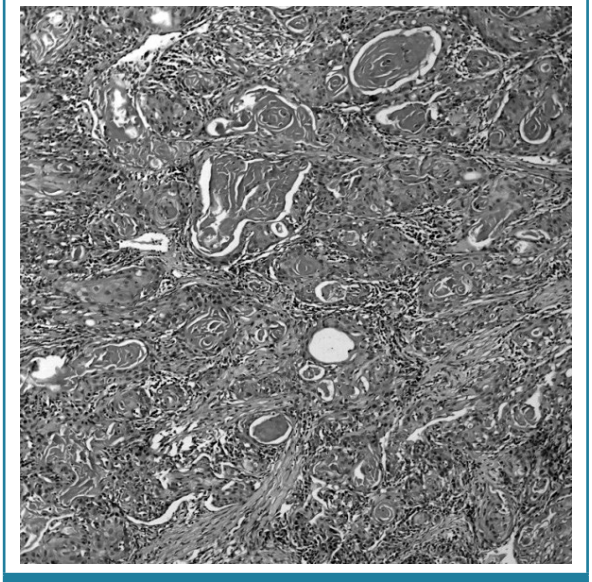

Figure 1: Well differentiated Squamous cell carcinoma. (Hematoxylene stain,100X)

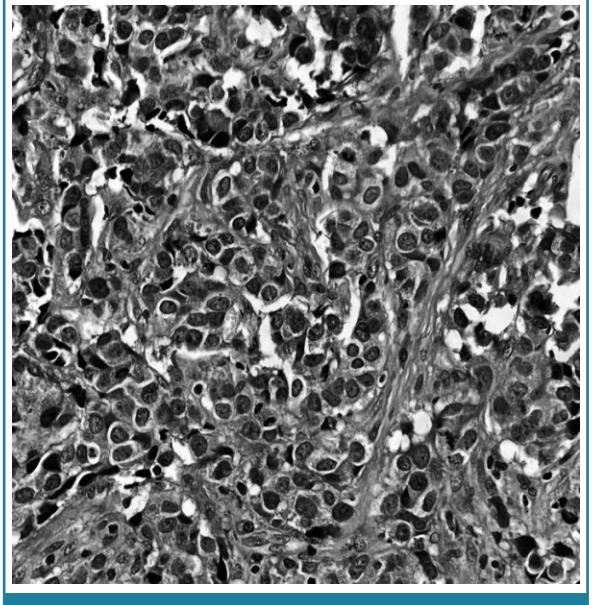

Figure 2: Moderately differentiated squamous cell carcinoma. (Hematoxylene stain, 400 X)

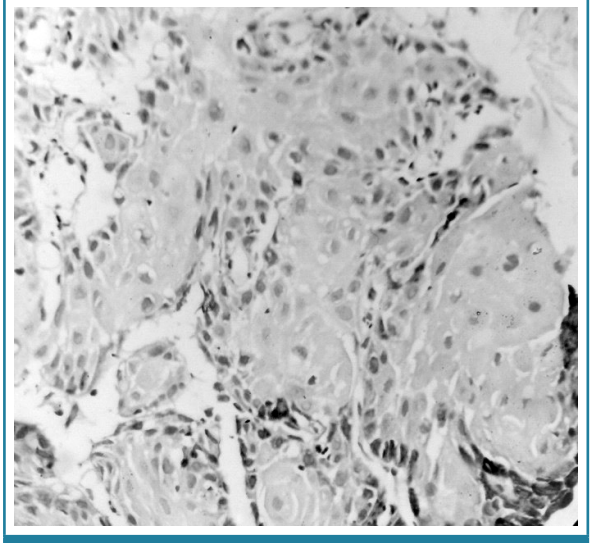

Figure 3: Picture showing focal P16 positivity with nucleus and cytoplasmic staining. (400 X) (P16 intensity score 1+)

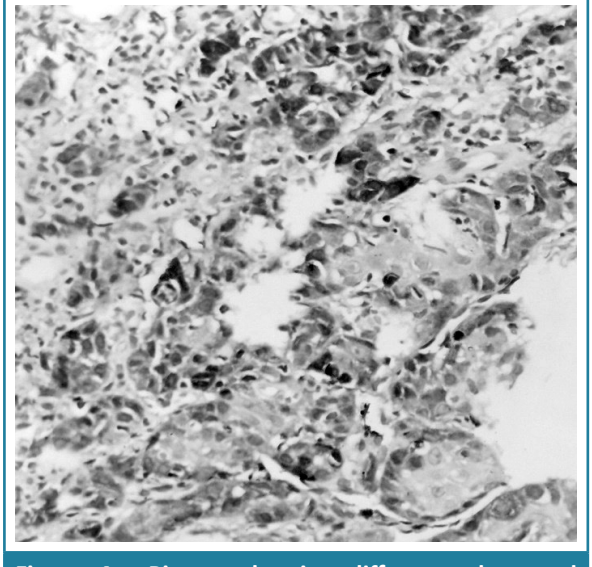

Figure 4: Picture showing diffuse nuclear and cytoplasmic staining of P16 in most of the area. (P16 intensity score 3+) (400 X)

DISCUSSION

Squamous cell carcinoma is the most common carcinoma in oral cavity and oropharyngeal carcinoma.[5] Our study also show squamous cell carcinoma as the most prevalent carcinoma in the oral cavity and oropharynx which is 97.8% (45 out of 46 tumours in the oral cavity and oropharynx). One case was of adenocarcinoma of palate.

In the retrospective 10 year study done by Tandon et al. more than 90% oral cancers were squamous cell carcinoma arising from the mucous membrane of oral cavity and oropharynx.[6]

Our study shows that most oral cavity and oropharyngeal carcinoma fall under age group 41-60 years and there is a male predominance in all age group. Mean age of presentation is 56.4. Male constituted 78.2 % and female constituted 21.8% in overall age wise. The youngest age of presentation of the carcinoma is 33 years of age and the eldest age is 88 years of age.

In the study of Ghazawi et al. the incidence of oral cavity cancer was 50-69 years of age group while for oropharyngeal carcinoma it was 60-69 years of age group.[7]

A retrospective study done by Taylor et al. shows higher rate of squamous cell carcinoma in males than female for both HPV positive and HPV negative HNSCC.[8]

A retrospective study done by Lee et al. consisted of 1910 males (93.4%) and 136 females (6.6%). The male-to-female ratio was 14:1 in this study.[9]

Smoking and alcohol intake had no role in p16 status of oral cavity and oropharyngeal carcinoma in our study. Out of 46 cases in our study, 24 smokers were p16 positive and 7 smokers were p16 negative. Similarly, 11 non smokers were p16 positive and 4 non smokers were p16 negative. (P>0.05) hence, smoking was not significantly correlated with p16 status of the patient. Similarly, 26 out of 46 cases were alcoholic with 18 case p16 positive and 8 cases p16 negative. 20 cases were non alcoholic out of which 17 showed p16 immunoreactivity and 3 were p16 negative.

Allameh et al. have studied the relation between p16 status and various clinicopathological parameters including smoking. The relationship of smoking habit with p16 status in OSCC revealed that the difference in p16 expression in smoker and non-smoker patients was not correlated with p16 expression levels. There was a significant decrease in p16 gene expression in smoker patients compared to non-smoker patients (p = 0.03).[10]

Saito et al. in their study observed an increase in the prevalence of p16-positive OPSCC, nonsmoker OPSCC, and nondrinker OPSCC in Japan between 2000 and 2011. Multivariate analysis identified p16 expression and alcohol consumption as significant, independent prognostic markers of OPSCC.[11]

In our study 15 cases consumed tobacco and all were p16 immunoreactive however for non tobacco consumer 20 were p16 immunoreactive and 11 were p16 negative. The total number of patient who did not consumed tobacco was high (31 over 15) and p16 positivity was also high for them.

The study done by Murthy et al. showed high prevalence of tobacco use in oral cancers (83.5%). High prevalence of tobacco use was seen in both p16 positive and p16 negative carcinomas with more p16 positivity in non-user of tobacco.[12]

Tobacco and alcohol are still the etiological factors for oral cavity cancers, however their role in etiology of oropharyngeal carcinoma is in decreasing trend with human papilloma virus as the emerging etiological agent in the causation of oropharyngeal carcinoma.[13]

Our study showed 38 (82.6%) cases out of 46 were present in the oral cavity and 8 (17.4%) of 46 cases were present in the oropharynx. Tongue was the most common site of carcinoma in both the oral cavity and oropharynx with anterior 2/3rd of tongue for oral cavity and posterior 1/3rd of tongue for oropharynx. There was random distribution of p16 expression in different subset of oral cavity tumor. Subset of oral cavity in our study included lip, tongue, gingivo buccal mucosa, buccal mucosa, floor of mouth, palate and retromolar trigone.

Squamous cell carcinoma (SCC) of the tongue is the most common oral cancer. Most cases occur on the lateral border of the tongue and only very rarely on the dorsum.[14]

A retrospective observational study done by Sharma et al. also found the most frequent oral cavity tumor to be tongue followed by buccal mucosa.[15]

A retrospective study done by Rikardsen et al. also showed mobile tongue as the most common site for oral squamous cell carcinoma.[16]

Our study showed good correlation of p16 with increasing grading of the tumor. 52.2% of the well differentiated carcinoma were p16 positive followed by 26.1% p16 negative. However, in moderately differentiated carcinoma and poorly differentiated carcinoma all the cases were p16 positive which comprised of 19.6% and 2.2 % of all the carcinoma respectively.

Grade is a strong and independent factor associated with distant metastasis in head and neck carcinomas. Thus, it adds important information to clinical and pathologic staging. It helps to identify patients at high risk for distant metastasis for whom an efficient systemic treatment is mandatory.

In the study of Ralli eta al., maximum number of cases belonged to Grade II (82.67%). Grade I and III tumors constituted 8% and 9.33% of cases, respectively. In their study, p16 expression had a significant correlation with histological grade of the tumor (P = 0.045). Out of 62 cases of Grade II (MDSCC), 25 (40.32%) cases showed strong p16 staining (Grade III), while only 11 (17.8%) cases were p16 negative. Out of 26 cases showing strong p16 staining (Grade III), maximum cases belonged to MDSCC category. Histological grade is a means of quantitating the degree of differentiation by applying a set of histological criteria. Usually welldifferentiated tumors are low grade lesions, whereas poorlydifferentiated tumors are high grade neoplasms.[17]

CONCLUSION

The most common cancer in oral cavity and oropharynx was squamous cell carcinoma. There was a male predominance in this type of tumor with male to female ratio of 3.5:1. The most common age group for the oral cavity and oropharyngeal carcinoma was between 41 years and 60 years. The common etiological factors for the carcinoma were tobacco chewing, smoking and alcoholism with human papilloma virus. The detection of HPV was done by demonstrating p16 immunohistochemistry. There was significant correlation between tumor, tumor grade and p16 immunohistochemistry ($p<0.005\%$). Hence p16 immunohistohemistry can be used as independent marker for HPV detection in oral cavity and oropharyngeal carcinoma.

RECOMMENDATIONS

HPV status assessment in the form of P16 immunoreactivity may be helpful in early identification of cancer, determination of prognosis and posttreatment follow-up. HPV status should be

included as an important risk and prognostic factor in future trials. Along with it, trials should be performed to get a proper treatment regime for HPV-positive and HPV-negative HNSCC in order to provide better treatment and lower relapse rates.

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The Profile of Infertility Couple at Kathmandu Model Hospital

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ABSTRACT

INTRODUCTION: To evaluate the demography and clinical profile of infertility couples attending OPD so that cause can be identified and treatment can be planned accordingly.

METHOD: This was a prospective observational study done at Gynaecology department, Kathmandu Model Hospital from March to June 2023. Total of 64 patients with infertility were included in the study. Semen analysis of male partner was done after 3 days of abstinence. Baseline pelvic ultrasound of female partner was done on the same day to rule out any pelvis pathology. On 2nd or 3rd day morning of menstruation blood test of female partner was done for basal follicle Stimulating Hormone (FSH), leutinizing hormone (LH), estradiol (E2), thyroid stimulating hormone (TSH), prolactin, antimullerian hormone (AMH) and Blood sugar. Hysterosalphingography (HSG) was done on 7-10th day menstrual cycle.

RESULT: The mean age of female was 31.26 years and male was 33.98 years. Primary infertility was 62.5% and secondary infertility was 37.5%.Female cause of infertility was highest 46.88%, male factor was 21.88%, both factor was 20.31% and unexplained was10.94%. Ovulatory dysfunction and tubal factor infertility was high. Men had normal semen analysis in 57.81% and asthenozoospermia was found in 28.13%.

CONCLUSION: In the present study, ovulatory dysfunction was leading cause of female infertility followed by tubal pathology. In male asthenozoospermia was commonest.

KEY WORDS: *Hysterosalpingography, Infertility, semen analysis.*

INTRODUCTION

Infertility is failure to conceive after unprotected intercourse for one year.[1] Primary infertility means the couple has never conceived, whereas secondary infertility means prior pregnancies have occurred, not necessarily live pregnancy.[2] Infertility affects about 10-15 % of reproductive age couple.[3] In our society child bearing is a social and family responsibility of a couple. In most of the time females face the pressure of infertility, resulting in depression. In urban society, late marriage, postponing childbearing due to studies and career infertility problems are increasing. In general infertility evaluation is done after failure to conceive in 1 year or if the age of woman is 35 years or more investigation is done in 6 months of unprotected intercourse.[3] Aneuploidy and poor pregnancy outcome is common after 35 years of age in women. The main causes of infertility are male factor 25%, Ovulatory 27%, Tubal/uterine 22%, others 9%, Unexplained 17%.[3] Before starting investigation complete history of the couple should be obtained. Attention to height, weight, body habitus, hair distribution, thyroid gland and pelvic examination should be given while examining female partner. Male partner should be examined by urologist if history suggests.[4]

The rationale of this study was to recognize reversible, treatable and modifiable risk factors and select patients for assisted reproductive technique and genetic counseling.

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The present study was designed to evaluate the demography and clinical profile of infertility couples attending OPD so that cause can be identified and treatment is planned accordingly.

METHOD

This was a prospective observational study done at Gynaecology department, Kathmandu Model Hospital from March to June 2023. Ethical approval was obtained from Institutional review Committee of phect-NEPAL Kathmandu Model Hospital. Data were collected in predesigned data collection proforma. Total of 64 couples with infertility were included in the study after obtaining informed consent. Those who refused to get enrolled were excluded from the study. Detail history of both partners was obtained. Physical examination of all the female partners was done at the clinic. Male partner was examined by urologist when required. Semen analysis of male partner was done after 3 days of abstinence. Semen was collected at the laboratory in a clean sterile container and analysis was done manually. WHO 2010 manual was followed.[5]

Baseline pelvic ultrasound of female partner was done on the same day to rule out any pelvis pathology. On 2nd or 3rd day morning of menstruation 10 ml of blood was drawn at the laboratory from the female partner for testing basal follicle Stimulating Hormone (FSH), leutinizing hormone (LH), estradiol (E2), thyroid stimulating hormone (TSH), prolactin, antimullerian hormone (AMH) and Blood sugar. Hysterosalpingography (HSG) was done on 7-10th day menstrual cycle at radiology department. Gastrograffin 70% dye was used. Azithromycin, hyoscine N butyl bromide and brufen were given 1 hour before the procedure. All the reports were collected on the proforma and later stored in excel sheet.

RESULT

A total of 64 couples with the diagnosis of infertility were included in the study. Those who did not return with reports were excluded. The mean age of female partner was 31.26 years and age range was 23-42 years. Male partner's mean age was 33.98 years with the range of 26-45 years. The highest number (37.50%) of males were in 31-35 years, females were (40.63%) in 26-30 years. Similarly lowest number of both males (7.81%) and females (1.56%) were in 41-45 years. Equal numbers of both partners were graduate (43.75%). Fifty percent of men were businessmen and 48.44% were service holder whereas 37.50% females were service holder and 20.31% were in business. None of the women were smoker, 70.71% were social alcohol drinker. Majority of men were smoker (70.71%) and social alcohol drinker ((62.50%). Smoking and alcohol has negative impact on semen. Most of the couples were suffering from primary infertility (62.50%) and 37.50% were having secondary infertility (Table 1). Highest number of women with primary infertility was in 26-30 years (29.69%) and secondary infertility was 31-35 years (15.63%).

Table-1: Socio-demographic features of infertility couples (n=64)

Variables	Male	Female
Age		
21-25	0	7 (10.45%)
26-30	16 (25%)	26 (40.63%)
31-35	24 (37.50%)	21(32.81%)
36-40	19 (29.69%)	9 (14.06%)
41-45	5 (7.81%)	1 (1.56%)
Education		
School	9 (14.06%)	19 (29.69%)
Higher secondary	13 (20.31%)	7 (10.45%)
Graduate	28 (43.75%)	28 (43.75%)
Master	14 (21.88%)	9 (14.06%)
Illiterate	0	1 (1.56%)
Profession		
Business	32 (50%)	13 (20.31%)
Service	31 (48.44%)	24 (37.50%)
Farmer	1 (1.56%)	0
Housewife	NA	27 (42.18%)
Alcohol		
No	17 (26.56%)	19 (29.69%)
Social	40(62.50%)	45 (70.31%)
Regular	7 (10.45%)	0
Smoking		
No	19(29.69%)	64 (100%)
Yes	45 (70.31%)	0
Duration of infertility		
1-3 years	43 (67.19%)	
4-6 years	17 (26.56%)	
7-9 years	3 (4.69%	
>9 years	1 (1.56%)	
Type of infertility		
Primary	40 (62.50%)	
Secondary	24 (37.50%)	

Investigations were done to find out the causes of infertility. Female cause of infertility was seen in 30 women (46.88%), male cause was seen in 14 men (21.88%), both male and female cause in 13 couples

(20.31%) and no cause was found in 7 couple (10.94%) (Fig 1).

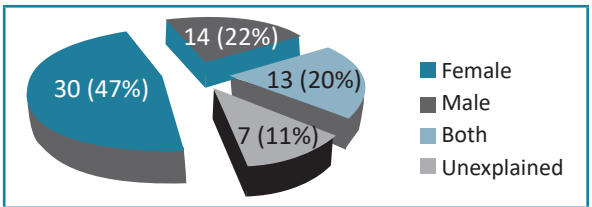

Figure 1: Causes of infertility

Semen of all the men was analyzed. Thirty seven (57.81%) had normozoospermia, 18 (28.13%) had asthenozoospermia, 2 (3.13%) had oligospermia, 5 (7.81%) had oligoasthenozoospermia, teratozoospermia and asthenoteratozoospermia was 1 in each (1.56%) (Table 2). Interestingly, no one was azoospermic. Twelve out of eighteen men with asthenozoospermia were smoker and all with oligospermia were also smoker.

Table-2: Semen analysis report

Age	Normozoo spermia	Astheno Zoo spermia	Oligo spermia	Oligo astheno zoospermia	Teratozoo spermia	Astheno terato zoospermia
26-30	9	3	1	3	0	0
31-35	12	10	1	2	1	0
36-40	14	3	0	0	0	0
41-45	2	2	0	0	0	1
Total	37 (57.81%)	18(28.13%)	2 (3.13%)	5 (7.81%)	1 (1.56%)	1 (1.56%)

Eleven (17.19%) of the women had one live birth and 13 (20.31%) had history of spontaneous abortion. None of the women were under weight, 26 (40.63%) had normal BMI, 28 (43.75%) were overweight and 10 (15.63) were obese. Most of the women (70.31%) had normal menstrual cycle and 29.69 % had oligomenorrhoea. Investigations results of female are shown in Table 3. AMH was in normal range in 37.5%, low in 23.44% and high in 39.06%. Five women had bilateral tubal block and 12 had one tube block as seen in hysterosalpingography. Pelvic ultrasonography showed uterine fibroids in 9.38%, endometriosis in 3.13%, PCOM in 17.19% and 3.13 % had ovarian tumour. Thyroid disorder was seen in 12 women.

Table 3: Investigations of female infertility

Variables	Frequency	Percentage %
AMH		
Normal (1.1-3.5 ng/ml)	24	37.50
Low (<1.1 ng/ml)	15	23.44
High (>3.5 ng/ml)	25	39.06
Hysterosalpingogram		
Normal	47	73.44
Bilateral tubal block	5	7.81
Right tubal block	7	10.94
Left tubal block	5	7.81
USG		
Normal	43	67.19
Fibriod	6	9.38
Endometriosis	2	3.13
PCOM	11	17.19
Ovarian tumors	2	3.13
Diabetes mellitus	2	3.13
Hyperprolactinemia	2	3.13
Thyroid disorder	12	18.75
SCH	7	10.94
Hypothyroid	5	7.81
Endometrial tuberculosis	1	1.56

Study of serum hormone level is important to find out the ovarian reserve, Ovulatory dysfunction and plan for treatment. Ovulatory dysfunction was found in 62.5%. The AMH was 4.304.32 ng/dl. Highest AMH was 22.14ng/dl at 33years of age and lowest at 0.019ng/dl at 37 years of age. Twenty five (39.06%) female had high AMH and 15 (23.44%) had low AMH. Twelve females with low AMH were above 31 years of age. Ovarian reserve declines with increasing age. Similarly hyperprolactinemia and thyroid disorder causes irregular menstrual cycle and anovulation. The mean hormone test result is shown in table 4.

Table 4: Serum hormone levels	
Hormone	**Mean** ± SD
AMH	4.30 ± 4.32 ng/ml
FSH	6.91 ± 2.03 mIU /ml
LH	8.53 ± 5.55 mIU /ml
Estradiol	32.85 ± 16.74 pg/ml
Prolactin	14.88 ± 9,86 ng/ml
TSH	2.96 ± 1.86 µIU/ml

DISCUSSION

Infertility problem is increasing, so a comprehensive evaluation is important for prevention and plan of treatment. There are many national and international studies on causes of infertility, investigations and treatment modalities. Study from Nigeria showed prevalence of infertility 15.7%. Secondary infertility was high (67%).[6] Where as in our study primary infertility (62.50%) was higher than secondary infertility (37.50%). This is comparable to other studies from Nepal[7,8] Saudi Arabia[9], Iran[10], Banbladesh[11,12] Srilanka[13] and Pakistan.[14] Poorly managed pelvic infection resulting in tubal block might be the cause in Nigeria as pelvic infection was seen in 78 % cases. Their semen analysis showed 12.6% were Azoospermia, 13% were severe oligospermia and 26.6% were asthenozoospermia. In our study no one was azoospermic, but asthenozoospermia was comparable. Another retrospective study showed 68% men had Azoospermia.[15] The most common findings in ultrasound were uterine fibroids (8.6%) and polycystic ovary (PCO) 8.6%. which was almost similar with the present study. HSG showed tubal blockage of almost similar result. The study did not include hormonal analysis.[6]

Pratima Neupane et.al studied causes of infertility at infertility centre in Kathmandu. Highest numbers of infertile females were in 20-30 years (51%) and similarly males were 31-35 years (45%) which is comparable to our study.[16] About 48.44% women were above 31 years, comparable to another study. Ovarian reserve declines with age resulting in infertility.[17]

Among females 37% had ovarian cyst, 15% had abnormal uterine bleeding, 9% had fibroids, 9.69% had pelvic infection, and 21.8% had thyroid disorder. In our study no one had abnormal uterine bleeding, we had only 3.13% ovarian tumour and thyroid disorder was similar. We did not rule out pelvic infection. Seventeen percent male had oligospermia, and 5.5% had Azoospermia. We found higher number (28.13%) of asthenozoospermia. Hormonal analysis and HSG were not included in this study.[16]

Study from Rajshahi city Bangladesh showed male and female at 25-34 years suffering from infertility were 51% each which is comparable to the present study. Higher education level was similar to our study (43.75%). Due to increase in literacy, marriage and child bearing is postponed, resulting in infertility. The studies showed 68% were trying to conceive for more than 5 years but in our study 67.19% were trying for 1-3 years.[18]

Study from Iran showed Ovulatory disorder (39.7%) and male factor (29.1%) as most common causes of infertility. other causes were endometriosis 8.2%, tubal 3.7%, unexplained 14.4%, more than one cause 17%.[19] Compared to this study, our study showed highest Ovulatory dysfunction (62.5%), second (26.56%) was tubal factor. lesser endometriosis (3.13%). This is similar to study from teaching hospital.[17] Our study had 46.88% female factor, 21.88% male factor, 20.31% both factor and 10.94% unexplained infertility. Female factor was commonest in other studies also.[11,20,21] Another retrospective study showed higher percentage of unexplained infertility, 48.4% in primary and 54.4% in secondary infertility. This may be due to limitation of investigations.[22]

In our study tubal cause of female infertility was second common but many studies from Pakistan and Bangladesh showed tubal pathology as leading cause of female infertility.[14,20]

High BMI, smoking and higher education was more common in infertile women in Iran.[19]

In our work all the women were non smoker and most were overweight with mean BMI of 26.30± 3.77. High BMI causes Ovulatory dysfunction and insulin resistance. Obese women may have regular menstrual cycle with infertility. The study showed 59.38% had high BMI comparable to another study.[17] High BMI causes menstrual irregularities. Women with overweight has one time and women with obesity has 4 times chance of infertility compared to normal weight.[23]

In the current study higher numbers of males were smoker (70.31%). Studies have shown that there is decline in semen volume, sperm concentration, motility and morphology with increase in number of cigarette smoked per day.[24]

CONCLUSIONS

Problem of infertility is increasing due to delaying marriage and child bearing for career and higher education. In the present study, ovulatory dysfunction is leading cause of female infertility followed by tubal pathology. In male single investigation was done as semen analysis.

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A Study to See Alterations in Morphology of Megakaryocytes in Bone Marrow Aspiration in Cases of Thrombocytopenia

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ABSTRACT

INTRODUCTION: The term thrombocytopenia is used when the platelet count is less than 150,000/microliter. It can be encountered in various hematological disorders i.e non-myelodysplastic hematological conditions to myelodysplastic syndrome.

AIM: The present study was undertaken to calculate the prevalence of various conditions that are associated with thrombocytopenia and to see the alterations in megakaryocytes morphology in bone marrow in various cases of thrombocytopenia.

METHODS: This study was a prospective series of 63 bone marrow aspiration conducted in Bir Hospital, NAMS in patients who presented with thrombocytopenia.

STATISTICAL ANALYSIS: The distribution of various morphological changes in cases on non-myelodysplastic conditions and myelodysplastic syndrome were compared using Chi-square test. A p-value less than 0.05 was considered significant.

RESULTS: In the present study, the commonest cause for thrombocytopenia for which bone marrow examination was sought was megaloblastic anemia, followed by acute leukemia and mixed maturation.

In non-myelodysplastic condition such as immune thrombocytopenia showed immature megakaryocytes, bare megakaryocytes, emperipolesis and cytoplasmic vacuolations in the megakaryocytes. Similar morphological features was observed in myelodysplastic syndrome as well.

CONCLUSION: Further studies on the evaluation of megakaryocytic alteration and their contribution to thrombocytopenia can provide growing knowledge to the pathogenesis of numerous hematopoietic disorders that may identify broader clinical applications of the newer strategies to regulate platelet count and functioning.

KEY WORDS: *Bone marrow, Megakaryocytes, Thrombocytopenia,*

INTRODUCTIONS

Platelets are formed and released into the bloodstream by precursors cells called megakaryocytes that are derived from the haemotopoietic stem cells, which evolve from the multipotential haemagioblast. Mature megakaryocytes give rise to circulating platelets by the acquisition of the cytoplasmic structural and functional characteristic necessary for platelet action[1], reaching cell sizes <50 -100 microns in diameter and ploidy ranging up to 128 N.[2] The hallmarks of megakaryocytes maturation are endoreduplication and expansion of cytoplasmic mass.[3] For the release of thousands of platelets from single megakaryocytes, it requires an intricate series of remodeling events. So, any abnormalities in this process can give rise to clinically significant disorders. Various factors can contribute to abnormal platelet counts, the most common one being inappropriate platelet production. The term thrombocytopenia means platelet count less

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than 150,000/ microliter can give rise to inadequate clot formation and increased risk of bleeding.[4] The thrombocytopenia can be encountered in various non-myelodysplastic conditions and myelodysplastic syndromes.[5]

Various studies have highlighted the dysplastic morphology of megakaryocytes in thrombocytopenia associated with myelodysplastic syndrome. Myelodysplastic syndrome are a heterogenous group of clonal hematopoietic stem cell disorders characterized by cytopenia(s), dysplasia in one or more cell lineage, bone marrow failure and increased risk of transformation to acute myeloid leukemia.[6] Megakaryocytes alteration have also been documented in some bone marrow aspiration in non-myelodysplastic syndrome.

The present study was undertaken to calculate the prevalence of various conditions associated with thrombocytopenia and to assess the megakaryocytic alterations in various cases of thrombocytopenia. The alteration can be dysplastic and non-dysplastic. Statistical analysis was applied to see if there was a significant difference in megakaryocytic alteration existed in non-myelodysplastic and myelodysplastic conditions.

METHODS

This was a prospective study of 63 cases of bone marrow aspiration of patient who presented with thrombocytopenia i.e platelet count less than 150,000/mm3 from November 2021 to October 2022 at Department of Pathology, National Academy of Medical Sciences (NAMS), Bir hospital, Kathmandu, Nepal. Written consent were obtained from all patients and confidentiality maintained throughout the study. Ethical approval was taken from IRB, NAMS.

The clinical details, including history, physical findings, complete blood counts, peripheral blood examination and other relevant laboratory investigations required were noted. The automated platelet count was further confirmed manually on peripheral blood smear which was stained in Leishmans' stain according to the guidelines in practical hematology. In subject with thrombocytopenia, the bone marrow aspirate from the posterior superior iliac spine were stained with Giemsa stain and examined under light microscope. (Olympus Pentahead BX53 model). Cases fulfilling the definition of thrombocytopenia but lacking marrow particle were excluded from the study.

The number of megakaryocytes was rated as following. Normal, if 1 megakaryocyte per 1 to 3 low power fields, increased, if more than 2 megakaryocytes per low power fields and decreased, if 1 megakaryocytes per 5-10 low power fields.[6]

Megakaryocytes morphology were studied with a 100X objective. Normal megakaryocytes have 4-16 nuclear lobes. Dysplastic features of megakaryocytes included multiple separated nuclei, micromegakaryocytes and hypogranular forms whereas non-dysplastic features included platelet budding, cytoplasmic vacuolation, immature forms, bare megakaryocytic nuclei, hypolobated forms, and emperipolesis. Micromegakaryocytes are defined as megakaryocytes whose size is similar to a large lymphocytes or monocytes and having single or bilobed nucleus whereas immature megakaryocytes are young megakaryocytes with scant bluish cytoplasm and devoid of nuclear lobe separation, occupying the most of the cell.[7] Hypogranular forms are megakaryocytes which have pale grey or water clear cytoplasm with sparse or no granules. The emperipolesis was considered depending on the engulfment of any one type of hematopoietic cells. The number and morphology of the megakaryocytes were assessed and documented. The data was analysed with SPSS version 16.

RESULT

The total number of 63 bone marrow aspirates cases that had thrombocytopenia were enrolled in this study. Male were 41 and female were 22. The ratio of male to female ratio 1.8:1.The peak age of presentation of thrombocytopenia was in 4th to 5th decade of life followed by 2nd to 3rd, 5th to 6th and 6th to 7th decade. The most common clinical features seen in case of thrombocytopenia was pancytopenia 40 cases, followed by bicytopenia 18 cases and thrombocytopenia 5 cases.

Table 1: Distribution of age in cases of thrombocytopenia

Age group in years	No. of cases	Cases in %
>15-24	05	07.93
25-34	09	14.28
35-44	07	11.11
45-54	17	27.0

55-64	09	14.28
65-74	10	15.87
75-84	06	09.52
>85	------	--------
Total	63	100

Table 2: Common causes for thrombocytopenia

BM/Clinical diagnosis	No. of cases	Percentage
Megaloblastic anemia	17	27.0
Acute Leukemia	09	14.2
Mixed maturation	08	12.69
Plasma cell myeloma	07	11.11
Hypocellular marrow	07	11.11
Myelodysplastic syndrome	03	04.76
Immune thrombocytopenia	03	04.76
Chronic lymphocytic leukemia	03	04.76
Chronic Myeloid Leukemia	03	04.76
Hairy Cell Leukemia	01	01.58
Hypersplenism	02	03.17

Megakaryocytes were normal in 4 cases of megaloblastic anemia and two cases each of multiple myeloma and hypocellular marrow. Decreased megakaryocytes were seen 13 cases of megaloblastic anemia followed by 8 cases of acute leukemia and 5 cases each of multiple myeloma and hypocellular marrow. Megakaryocytes were increased in 7 cases with mixed maturation and cases of immune thrombocytopenia. In 2 cases of hypersplenism observed, there were normal megakaryocytes.

Table 3: Number of Megakaryocytes in different causes of thrombocytopenia

No. of Causes of thrombocytopenia	Normal (1MK/1-3LPF)		Megakaryocytes/ LPF Increased >2MK/ LPF	Decreased 1MK/ 5-10LPF
Megaloblastic anemia	No. 4	% 24	No. % 0 0	No. % 13 76
Acute leukemia	1	12	0 0	8 88
Mixed maturation	1	12	7 88	0 0
Plasma cell myeloma	2	28	0 0	5 72
Hypocellular marrow	2	28	0 0	5 72
Myelodysplastic syndrome	1	34	0 0	2 66
Immune thrombocytopenia	1	34	2 66	0 0
Chronic lymphocytic leukemia	1 34		0 0	2 66
Chronic Myeloid Leukemia	1 34		0 0	2 66
Hairy cell Leukemia	0 0		0 0	1 2.6
Hypersplenism	2 100		0 0	0 0
TOTAL	16		9	38

In the present study, it was found that megakaryocytes were decreased in 76% and normal in 24% cases of megaloblastic anemia. Similarly, in acute leukemia, megakaryocytes were decreased in 88% and normal in 12 % cases. In cases of immune thrombocytopenia, increased megakaryocytes were seen in 66% and normal in 34%.

Cases with mixed maturation showed increased megakaryocytes in 88% and normal in 12% of cases.

Among the different morphological alterations of megakaryocytes in bone marrow, hypolobated forms were seen mainly in megaloblastic anemia i.e 14 cases, followed by acute leukemia, mixed maturation, multiple myeloma, chronic lymphocytic leukemia and chronic myeloid leukemia 3 cases in each. Nuclear lobe separation were seen in 8 cases of megaloblastic anemia followed by 3 cases each of mixed maturation and multiple myeloma and chronic lymphocytic leukemia.

Bare megakaryocytes were seen in 4 cases of megaloblastic anemia followed by 3 cases each of acute leukemia, immune thrombocytopenia and chronic myeloid leukemia. Immature forms were seen mainly in acute leukemia i.e 4 cases followed by Myelodysplastic syndrome and immune thrombocytopenia 3 cases each. Emperipolesis was seen in 2 cases of immune thrombocytopenia. Cytoplasmic vacuolization were seen in myelodysplastic syndrome and immune thrombocytopenia 2 cases each.

Table 4: Altered morphology of megakaryocytes for different causes of thrombocytopenia

	MA	AL	MM	MY	MDS	ITP	CLL	CML	HCL	HS	TOTAL
Hypolobated	14	3	3	3	1	1	3	3	2	2	35
Immature		4	2	1	3	3					13
Micromegakaryocyte						1		3			4
Hypogranular			2			1					3
Emperipolesis					1	2					3
Nuclear lobe separation	8	2	3	3		2	3		2	2	25
Platelet budding						1					1
Bare megakaryocyte nuclei	4	3	2	2	1	3		3			18
Cytoplasmic vacuolisation					2	2					4

(MA: Megaloblastic anemia, AL: Acute leukemia, MM: Mixed maturation, MDS: Mylodysplastic syndrome, ITP: Immune thrombocytopenia, CLL: Chronic lymphocytic leukemia, CML: Chronic myeloid leukemia, HCL: Hairy cell leukemia, HS: Hypersplenism)

DISCUSSION

Thrombocytopenia is frequently encountered in complete blood count examination for which bone marrow examination is done to look for any alteration in megakaryocytes number and morphology. The bone marrow aspirate is stained using Giemsa stain to see any alteration in megakaryocytes number and morphology. This help to diagnose underlying hematological disorder.

In the present study, thrombocytopenia was seen in all age groups with a minimum age of 15 years to maximum age of 80 years. Male to female ratio is 1.8:1. This similar to study done by Vinayakamurthy et al.[7]Out of 63 cases of thrombocytopenia, maximum number of cases i.e 17 cases i.e 27% were of 4th to 5th decade of life. This was followed by 9 cases of 2nd to 3rd , 5th to 6th and 6th to 7th decade of life.

Thrombocytopenia was more common in male 43 cases and female 20 cases. The commonest cause of thrombocytopenia for which bone marrow examination was sought was megaloblastic anemia 17 cases (26.56%) followed by acute leukemia 9 cases [7](14.06%). Our findings are similar to study done by Muhury et al.[5] who found acute leukemia the most common cause for thrombocytopenia which may be due to infiltration of the marrow by the leukemic cells.

Other causes were mixed maturation 8 cases (12.50%), plasma cell myeloma 7 cases (11.0%) and hypocellular marrow 7 cases (11%). Least cases were seen of hypersplenism 2 cases(3.1%) and Hairy cell leukemia 1 case (1.5%).

Among the varied morphological features observed, hypolobated megakaryocytes were in 40%, nuclear lobe separation in 32%, bare megakaryocyte nuclei in 22% cases of the megaloblastic anemia. Similarity exist in study observed by Wickramasinghe et al.[8] their cell kinetics and their capacity to synthesize protein. These abnormalities are maximal in the last dividing cell class and in non-dividing cells, presumably because B12 and folate uptake is largely confined to the most immature erythroid and granulocyte precursors. In patients with moderate or severe anaemia due to B12 or folate deficiency, erythropoiesis is markedly ineffective; intramedullary cell death occurs mainly in the early and late polychromatic megaloblasts. The damaged erythroblasts appear to display neoantigens or normally-hidden antigens at their cell surface and these react with naturally occurring antibodies. The opsonised erythroblasts are then recognised by macrophages via their IgG-Fc receptors and phagocytosed. Marrow cells from B12- or folate-deficient patients show a subnormal suppression of 3H-thymidine incorporation after pre-incubation with non-radioactive deoxyuridine, suggesting that such cells suffer from an impairment of the 5,10-methylene-THF-dependent methylation of deoxyuridylate to thymidylate. However, the exact mechanism by which B12 deficiency causes a reduced supply of this folate coenzyme is uncertain. Methylcobalamin is required for the 5-methyl-THF-dependent methylation of homocysteine to methionine and an impairment of this reaction will result in both reduced conversion of 5-methyl-THF to THF and in reduced methionine synthesis. There is controversy as to whether the reduced supply of THF or methionine is responsible

for the reduced availability of 5,10-methylene-THF. Currently, the balance of evidence favours the hypothesis that the reduced supply of methionine leads to reduced synthesis of formyl-THF and, eventually, of 5,10-methylene-THF. Despite the evidence for impaired thymidylate synthesis, the duration of the S phase of megaloblasts appears to be normal or only modestly increased. Data on rates of DNA strand elongation are inconsistent, with subnormal rates reported in PHA-stimulated B12- or folate-deficient lymphocytes and normal rates in B12- or folate-deficient bone marrow cells. Recent studies have shown that HL60 cells grown in B12- or folate-deficient medium and B12- or folate-deficient megaloblastic bone marrow cells misincorporate uracil in lieu of thymine into DNA. Excision of misincorporated uracil without repair and, possibly, slowing of the movement of DNA replication forks may lead to an arrest in the progress of cells through the cell cycle. Recent in vitro data suggest that some of the arrested cells may suffer apoptosis. The biochemical basis of the characteristic stippled appearance of nuclei in B12 or folate deficiency remains speculative. Similarly, acute leukemia cases showed immature megakaryocytes in 30.4%, followed by bare megakaryocytes 16.6% and nuclear lobe separation in 8% of cases.

Multiple myeloma showed hypogranular form in 66.66%, followed by immature form 15.3%, nuclear lobe separation in 12%, bare megakaryocyte nuclei 11.11% and hypolobated forms in 8.5%. Hypolobated form was observed in almost all cases like megaloblastic anemia, acute leukemia, multiple myeloma, mixed maturation, immune thrombocytopenia, leukemia and hypersplenism. This attributed to diminished DNA synthesis and increased ploidy leading to nuclear maturation defect.

Myelodysplastic syndrome also showed various alterations like cytoplasmic vacuolation in 50%, emperipolesis in 33%, hypolobated forms in 8.5%, immature form in 7.69% and bare megakaryocyte nuclei in 5.5%.

Cases of chronic myeloid leukemia also showed alterations in the form of micromegakaryocytes, hypolobated forms and bare megakaryocytic nuclei.

Megakaryocytes were normal in 4 cases of megaloblastic anemia and two cases each of multiple myeloma and hypocellular marrow. Decreased megakaryocytes were seen 13 cases of megaloblastic anemia followed by 8 cases of acute leukemia and 5 cases each of multiple myeloma and hypocellular marrow. Megakaryocytes were increased in 7 cases with mixed maturation i.e 88% and cases of immune thrombocytopenia i.e 66%.[9] Similar observation was done by study conduected by Shi et al.[10] In 2 cases of hypersplenism, there were normal megakaryocytes. Similarly, in acute leukemia, megakaryocytes were decreased in 89% and normal in 12 % cases. In acute leukemia, megakaryocytes were decreased in 88% of cases, similar to Pokharel S et al[9] and Dameshek W et al.[11]

Different morphological alteration of megakaryocytes in the bone marrow due to myelodysplastic syndrome or non-myelodysplastic syndrome carries value and brings special interest in country like ours with limited resources as we lack facility for sophisticated megakaryocyte studies like culture, specific marker, electron microscope for ultrastructural details.

This study showed that the diagnostic accuracy for different causes of thrombocytopenia can be enhanced by correlating different alteration in megakaryocytes morphology and number that were observed in the bone marrow aspirate.

CONCLUSION

There are many similarities in morphological changes of megakaryocytes among different hematological diseases; never the less, the diagnostic approach will vary when detailed knowledge about morphological changes of megakaryocytes is available. In this study, increased megakaryocytes count and presence of bare megakaryocytic nuclei and hypolobated forms were found to be significant in immune thrombocytopenia. Understanding of different morphological changes of megakaryocytes in the bone marrow aspirates can improve the diagnostic accuracy for a wide range of hematological disorders there by enabling proper therapeutic interventions.

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Comparison of Post-Operative Pain after Single Visit Root Canal Filling using Resin Based Sealer and Bioceramic Sealer

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ABSTRACT

INTRODUCTION: The incidence of postoperative pain after the root canal treatment is reported to range from 3%-58%. The intensity and duration of postoperative pain after single visit root canal treatment are subjective and multifactorial. The main objective of this study was to compare the postoperative pain following single visit root canal treatment using a resin based sealer and bioceramic sealer.

METHODS: This is a prospective comparative interventional study. 88 patients requiring root canal treatment were selected for the study, 44 in each sealer group. Single visit root canal treatment was carried out using standard protocol and root canals were filled using gutta percha and either resin based sealer or bioceramic sealer. The patient were informed to register their post-operative pain in a visual analog scale ranging from 0 to 10 at 4hours,24 hours and 48 hours intervals. Postoperative VAS score between the groups were compared using independent t-test and paired t-test.

RESULTS: There was no significant difference in postoperative pain among two sealer groups, however, a reduction in pain was seen in each group with time. When the association between demographic and clinical characteristics with postoperative Pain was checked, only preoperative pain was found to be related to postoperative pain in both the groups.

CONCLUSION: There was no difference in incidence and intensity of postoperative pain among a resin based sealer and a bioceramic sealer.

KEY WORDS: *Bioceramic sealer, postoperative pain, resin-based sealer, Root canal filling*

INTRODUCTION

The incidence of postoperative pain after the root canal treatment is reported to range from 3%-58%.[1] The intensity and duration of postoperative pain after single visit root canal treatment are subjective and multifactorial which includes age, gender, systemic diseases, pulpal status, preoperative pain level, number of roots, the choice of instrument, the choice of root canal sealer etc.[2-5]

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After the proper cleaning and shaping procedures root canal systems are obturated with gutta –percha and endodontic sealer which must be confined within the root canal system. However, the sealer placed in the root canals interfere with the periodontal tissues through the apical foramen and additional lateral canals. The physical and chemical properties of the sealer, such as pH-level, consistency etc., affect the intensity of local inflammatory reactions in these tissues resulting in post-obturation pain.[6-7]There are different types of sealers available based on their compositions and properties.

Resin-based sealer is frequently used because of its favorable physicochemical properties and adaptability to root canal walls.[8] Bioceramic sealer is a newer sealer

that has gained popularity due to its biocompatibility, antimicrobial and bioactive properties helping in periapical healing. They are less cytotoxic than resin based sealer.[9, 10] Due to these potential benefit of bioceramic sealers over resin based sealer it can be considered to have lesser incidence and intensity of postoperative pain than resin based sealer. However there were limited studies evaluating potential impact of bioceramic sealer to resin sealer on postoperative pain and to the best of our knowledge none had been documented in our country.

Hence, the main aim of this prospective comparative interventional study was to compare the incidence of postoperative pain after single visit root canal treatment using resin-based (AH plus) and Bioceramic (Ceraseal) sealer.

METHOD

Patient selection and pre-treatment assessment

This is a prospective comparative interventional study done in conservative dentistry and endodontics unit, Department of dental surgery, NAMS, Bir Hospital .The ethical clearance was taken from institutional review board. The study was conducted from October 2022 to May 2023. A total of 88 patient were selected based on inclusion and exclusion criteria and divided equally into two groups.

Patients visiting the dental clinic of age 18 and above with tooth requiring nonsurgical root canal treatment were included. The written informed consent was taken from all the patient included in the study. The exclusion criteria were:

1. Patient with medical history with ASA class III/IV
2. Patient taking analgesic, anti-inflammatory medication, or antibiotic with in the 7 days prior to the beginning of treatment
3. Teeth with resorptions and calcification
4. Teeth with periodontal problems
5. Non restorable teeth

After a through clinical and radiographic evaluation single visit root canal treatment was done by the same faculty of conservative dentistry and endodontic unit. Prior to the treatment, patients were instructed about visual analogue scale (VAS) to determine their pain scores. Preoperative pain levels were recorded.

Root canal treatment procedures

In all the patients, teeth were anaesthetized using 2% lidocaine containing 1: 100000 epinephrine. For the maxillary teeth, slow local infiltration in the buccal vestibule or posterior superior alveolar nerve block was given. For the mandibular teeth, an inferior alveolar nerve block and lingual nerve block was used.

All teeth were isolated with rubber dam and the procedure was performed under a dental operating microscope. After removal of caries, endodontic access preparation was done with sterile diamond bur. The working length was determined with an apex locator and confirmed radiographically. A glide path was prepared with #10 k file and the canals were prepared by 0.04 taper Hyflex CM files (Coltene/Whaledent Inc, USA) according to the manufacturer instruction. Canals were irrigated with 3% sodium hypochloride, 17% EDTA. Normal saline was used to flush in between the two irrigants and as a final irrigant. After confirmation of the master cone radiograph, canals were dried with paper points and obturated with sigle cone technique using either resin sealer i.e. AH plus sealer (Dentsply DeTrey GmbH, Germany) and gutta percha or bioceramic sealer i.e. Ceraseal sealer (Meta Biomed, South Korea) and gutta percha. Then the access cavity was closed with temporary cement. Post-obturation radiographs was taken and evaluated for the presence or absence of sealer extrusion from the root canal system.

Pain assessment

After completion of root canal filling the patients were instructed about VAS and asked to rate their pain on a Visual analogue scale (VAS) at the duration of 4 hours, 24 hours, and 48 hours. Patients was instructed to take 1000mg acetaminophen in case of severe pain and asked to record the dose and time on the survey. They were contacted on phone by the principal investigator to remind them register their pain according to specified time. They were instructed to return the questionnaire at the second appointment after 48 hours when coming for follow up and permanent restoration.

Statistical analysis

Statistical analysis of the data was performed with R version 4.3.1. Postoperative VAS score between the groups were compared using independent t-test

and paired t-test. A linear regression analysis was performed to find the association of postoperative pain with age, gender, and tooth location, number of roots, vitality, preoperative pain and sealer extrusion.

RESULTS

A total of 88 patients, 44 in each group participated in the study. Out of 88, 53 were female and 35 were male. The age ranged from 18 years to 75 years with mean SD: 36.18± 13.6 years. The demographic and clinical characteristics of the patient are presented in Table 1. All the presented characteristics showed no statistically significant differences among two sealer groups. When the association between these characteristics with postoperative was checked, only preoperative pain was found to be related to postoperative pain in both the groups (Table 2). There was no significant difference in postoperative pain among two groups, however, a reduction in pain was seen in each group with time (Table 3). There is a significant reduction in pain after 4 hours of root canal treatment but statistical significance was not seen in 24 hours and 48 hours among the each groups (Table 4). In the AH plus group, the reduction of pain was 91.6% whereas in the BC group it was 92.3% after 48 hours (Table 4). The mean reduction of pain was higher in BC group than AH plus group as shown in Figure 1.

Table 1. Demographic and Clinical Characteristics for Post-operative VAS Score

Clinical Characteristics		Resin based sealer Group n=44	Bioceramic sealer group n= 44
Age	**mean±sd**	**36.8±12.7**	**35.6±14.6**
Gender	Female	28	26
	Male	16	18
Vitality	No	26	23
	Yes	18	21
Sealer Extrusion	No	41	43
	Yes	3	1
Number of roots	M	35	26
	S	9	18
Location	Mandible	19	19
	Maxilla	25	25
Preoperative pain	No pain	32	31
	Pain	12	13

Table 2: Regression Analysis of postoperative pain

Variable	Coeffi-cient	Standard Error	t-value	P-value
Preoperative VAS	0.31	0.04	6.52	<0.001
Age	0.011	0.009	1.25	0.21
Gender	-0.254	0.25	-0.99	0.321
Sealer	-0.215	0.24	0.895	0.374
Vitality	-0.301	0.245	-1.228	0.223
Location	0.047	0.252	0.188	0.851

Table 3. Comparison of pain Intensity preoperatively and Post operatively between Resin based sealer and Bioceramic sealer groups.

Vas Score	Resin based mean±sd	Bioceramic mean±sd	P-value
Preoperative	1.55±2.65	1.57±2.60	0.967
After four hours	0.591±1.40	0.318±1.22	0.3325
After 24 hours	0.227±1.08	0.205±0.851	0.912
After 48 hours	0.045±0.302	0.045±0.302	NA

Table 4: Test of significance of Resin based sealer Group and Bioceramic sealer Group

Time	mean±sd	Mean difference	t-value	p-value
Bioceramic sealer group				
Preoperative	1.57±2.60			
Four hours	0.318±1.22	1.25	3.78	<0.001
24 hours	0.205±0.851	0.113	0.81	0.41
48 hours	0.045±0.302	0.15	1.73	0.089
Resin based sealer group				
Preoperative	1.55±2.65			
Four hours	0.591±1.40	0.95	2.98	0.0047
24 hours	0.227±1.08	0.36	1.48	0.146
48 hours	0.045±0.302	0.18	1.27	0.209

Table 5: Reduction in pain

VAS score	Resin based sealer			Bioceramic sealer		
	No pain	Pain	Pain im-prove-ment	No pain	Pain	Pain im-prove-ment
Preopera-tive	32	12		31	13	
After four hours	37	7	41%	41	3	76%
After 24 hours	41	3	83%	42	2	92%
After 48 hours	43	1	91.6%	43	1	92.30%

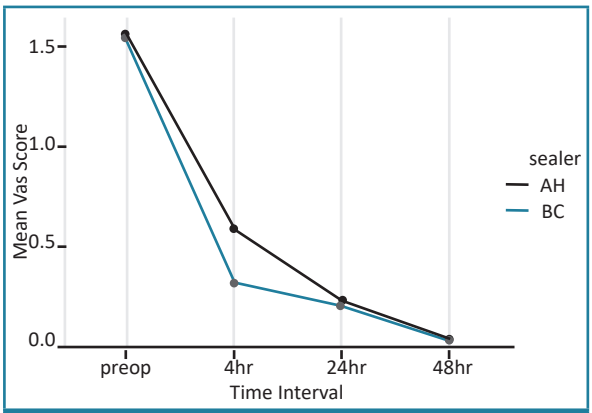

Figure 1:Mean VAS to Time Interval

Resin based sealer(red line)

Bioceramic sealer(blue line)

DISCUSSION

In this study single visit root canal treatment was carried out and the protocol was same in both groups except for the sealer used. Single visit root canal treatment was preferred because of the time efficiency both to the patient and the clinician and also to avoid inter-appointment flare ups. In the previous studies it has been observed that post-operative pain levels between single and multiple visits did not differ .[11] In this study Visual Analogue Scale (VAS) was used as an instrument to evaluate pain which is similar to several endodontic studies on postoperative pain.[11-13]The postoperative pain following the single visit root can treatment was observed at 4 hours, 24 hours and 48 hours. The 4 hours VAS was chosen to exclude the effect of local anesthesia. Also the postoperative pain declines significantly after 48 hours, hence 48 hours VAS was taken as final postoperative pain score in this study.[12]

Post-operative pain is not confined to a single factor, rather it may be associated with several factors like age, gender, tooth location, number of root, pulp vitality, preoperative pain, obturation material and technique, sealer extrusion etc.[13,14] In the present study, multiple logistic regression analysis was conducted to determine the effect of these factors on pain incidence. There was no association of postoperative pain with any of these factors except for the preoperative pain. Some studies have found association of postoperative pain with patient related factors including age and gender and some have not.[13-19] In the present study, there was no significant association of age and gender with postoperative pain. Similarly there was no association of tooth location and pulpal status (vitality) with postoperative pain which was similar to other studies.[18, 20] In contrary to previous studies there was no association between number of roots and postoperative pain in our study.[20, 21]

However, there was a relation between preoperative and postoperative pain. In this study 27% cases in resin based sealer group and 29% in bioceramic sealer group had preoperative pain. The postoperative VAS score reduced gradually with time in both the groups. The mean reduction in pain after 4 hours of obturation was more in bioceramic sealer group compared to AH plus sealer but there were no differences in 24 hours and 48 hours. This signified that, the postoperative pain was not related to the sealer type. This result was similar to many previous studies comparing the postoperative pain between resin based sealer and bioceramic sealer.[18-20]

In the present study, the sealer extrusion was seen in 3 cases in resin-based sealer group and 1case in bioceramic sealer group. But none of these cases showed increased postoperative pain. This is in contrary to different previous studies which had shown association of sealer extrusion with postoperative pain.[15] The reason behind may be the amount of sealer extrusion which was very less to cause any inflammatory reaction and pain.[18, 21, 22] Less sealer extrusion may be attributed to precise working length determination using an electronic apex locator along with IOPA radiograph, cleaning and shaping technique thus avoiding over-instrumentation and overfilling. Another factor could be that all the cases were primary treatment cases, not retreatment cases and hence had lesser chances of over instrumentation of canals.[19]

CONCLUSION

Within the limitation of our study it can be concluded that there was no difference in intensity of postoperative pain among a resin based sealer and a bioceramic sealer. Post-operative pain was not affected by age, gender, tooth location, pulp vitality, number of roots and sealer extrusion but only associated with preoperative pain.

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Outcome of Ventilatory Supports in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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ABSTRACT

INTRODUCTION: Chronic obstructive pulmonary disease (COPD) leads to significant morbidity and mortality and is the third leading cause of death in the world. The patient having an episode of acute exacerbation of chronic obstructive pulmonary disease (AE of COPD) may require hospital admission including intensive care unit (ICU) admission due to respiratory failure.. Ventilatory support have shown significant outcomes in recovery of the patients. There are limited studies on this subject in Nepal and in our region.

METHODS: This retrospective study was conducted to describe clinical profile of patients diagnosed with AE of COPD in Chitwan Medical College Teaching Hospital (CMCTH), a tertiary care centre in Nepal during 1year period from February, 2022 to January, 2023. Data were collected from hospital medical records. All cases of AE of COPD were included in this study after excluding patients with primary diagnosis of restrictive lung disease causing hypercapnia and patients being treated with non-invasive ventilation (NIV) and continuous positive airway pressure (CPAP).

RESULTS: A total of 502 cases presented to our hospital during the one year period. Among them, 64.4% were female. Most of the patients belonged to the age group of 50-80 years. 24.30% were under ventilatory supports. Among all patients (122) under ventilatory supports, 56.55% patients were under non-invasive ventilation (NIV) and 43.44% were under invasive mechanical ventilation (IMV). 21% patients left against medical advice (LAMA), 25% on discharge on request (DOR), 51.99% patients were discharged with full recovery, whereas mortality with treatment was 2.19%.

CONCLUSION: Patients with AE of COPD were admitted in significant numbers which was seen more prevalent in females and older age group. Ventilatory support is widely used in the management, with NIV being more preferred over IMV and has proven to be effective in reducing complications and mortality rate.

KEY WORDS: *AE of COPD, Ventilation*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common respiratory illness characterized by airflow limitation and inflammation of the airways. COPD is the third leading cause of death worldwide, and it is a leading cause of morbidity as well.[1] Smoking is the major environmental risk factor for COPD. Other risk factors include exposure to secondhand smoke, including indoor biomass smoke, and air pollution.[2,3]

Ventilatory support is a life-saving procedure for patients with selected cases of acute exacerbation of COPD. Noninvasive ventilation (NIV) is the mainstay of treatment during such exacerbations, while invasive mechanical ventilation (IMV) is reserved for more

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severe cases. Both NIV and IMV have been shown to reduce mortality and improve quality of life in patients with COPD.[4,5]

Acute exacerbations (AE) are episodes of worsening COPD symptoms that can lead to hospitalization and death. Early identification and treatment of exacerbations can help to prevent complications and improve outcomes and is therefore an essential pre-requisite for optimal outcomes. (6).

This study aimed to describe the clinical profile of patients with acute exacerbation of COPD and the treatment outcomes.

METHODOLOGY

Study Design

This is a retrospective study conducted in Chitwan Medical College Teaching Hospital (CMCTH), a tertiary care teaching hospital in central Nepal, in patients diagnosed with AE of COPD from February 2022 to January 2023.

Study Population:

The study population consisted of all patients diagnosed with AE of COPD admitted to CMCTH during above mentioned period. The exclusion criteria were: patients with primary diagnosis of restrictive lung disease causing hypercapnia and patients being treated with NIV or Continuous positive airway pressure (CPAP).

Data Collection

Data on patients' demographic variables, treatment and outcome were collected from patients' medical records. This study was approved by the ethical committee of our institution [Mention the body providing the ethical approval, date and reference number of ethical approval].

Statistical analysis:

The collected data were entered organized in Microsoft Excel. Data analysis was performed using IBM SPSS (Statistical package for Social Sciences) version 21 and data are presented as count or and percentage.

RESULT

Among 502 patients, there were 322 (64.14%) females with a ratio of 1.78. The mean age of the patients was 72.67±9.21 years. Most patients belong to the age group of 50-80 years (Table 1).

Table 1. Age distribution of patients with COPD (n=502)

Age (Years)	n (%)
Up to 40	2 (0.39)
41-50	5 (0.99)
51-60	38 (7.56)
61-70	177 (35.25)
71-80	180 (35.85)
81-90	90 (17.92)
>90	10 (1.99)

Shortness of breath 483 (96.21%) was the most common clinical presentation followed by cough 310 (61.75%) and fever 118 (23.50%) (Table 2).

Table 2. Clinical presentation of patients with COPD (n=502)

Clinical presentation	n (%)
Shortness of breath	483 (96.21)
Cough	310 (61.75)
Fever	118 (23.50)
Swelling of body	35 (6.97)
Altered sensorium	24 (4.78)

Smoking was the most common risk factor of COPD. In our study, 128 (25.49%) patients currently used some form of smoking whereas 328 (65.33%) were past smoker (Fig ~~2~~1 and table 3). Non-smoker who developed COPD was probably due to prolonged exposure to domestic smokes.

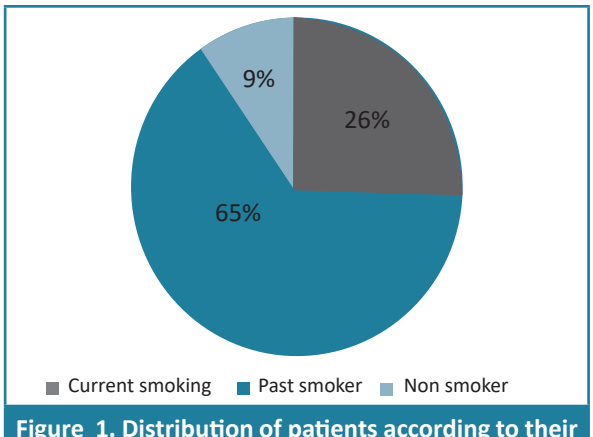

Figure 1. Distribution of patients according to their smoking status (n=502)

Among 502 patients, 261 (51.99%) were discharged normally whereas 11 (2.19%) died during their hospital stay (Fig ~~3~~2)

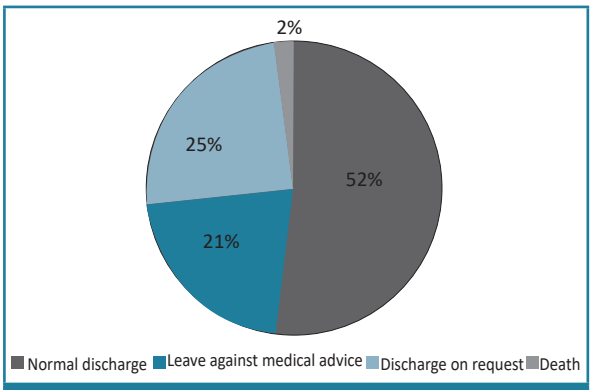

Figure 2. Distribution of patients according to outcome (n=502)

Among 502 patients, 122 (24.30%) patients were under ventilatory support. Out of 122, there were 69 (56.55%) patients under non-invasive ventilation (NIV) and 53 (43.44%) under invasive mechanical ventilation (IMV) (Fig ‡ 3).

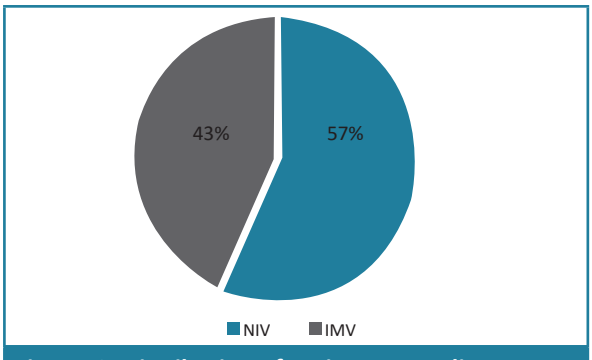

Figure 3. Distribution of patients according to type of ventilation support (n=122)

Out of 122 patients on ventilatory support, there were 55 (45.08%) male and 67 (54.92%) female. The mean hospital stay and ICU stay among the patients with ventilatory support was 5.48±3.48 and 4.40±3.10 days respectively and was higher than those without ventilatory support. Similarly, among 11 cases of in-hospital mortality, 6 (54.54%) were under ventilator support.

Table 3. Distribution of demographic and clinical variables in patients with and without ventilatory support.

Variables	Ventilator support	
	Yes	No
Age	73.32±9.40	72.46±9.15
Gender		
Male	55	125
Female	67	255
Smoking status		
Current smoker	25	103
Nonsmoker	9	38
Past smoker	88	240
Hospital stays (days)	5.48±3.48	4.21±2.45
ICU stays (days)	4.40±3.10	1.34±1.98
Mortality	6	5

DISCUSSION

COPD is one of the major public health problems worldwide and acute exacerbation contribute substantially to morbidity and mortality.[7] In many cases, mostly in severe cases of AE of COPD, despite pharmacological treatment, ventilatory supports are necessary. Ventilatory supports are life-saving procedures and have shown significant improvement in morbidity and mortality rates in AE of COPD patients.[4,5]

In our study, we found higher incidence of AE of COPD in female (64.14%) which is similar to studies shown by.[2,3] Most patient (35.85%) belonged to age group 50-80 years which is similar to other studies.[8] of the patients were found to have smoking history where, 25.49% were active smoker and 65.33% were past smokers. Similar findings were also seen in other studies.[2,3,8]

The most common clinical presentation was shortness of breath (96.21%) followed by cough (61.75%) and fever (23.50%). Other common clinical features were swelling of the body and altered sensorium. Among the patients that were admitted, 25% of patients with AE of COPD required ventilatory support, among which 56.55% were under non-invasive ventilation (NIV) and 43.44% were under invasive mechanical ventilation (IMV). Similar findings were found in other study.[9]

Among all the patients that were admitted, 52% made full recovery and were discharged normally whereas mortality was 2.19%. Among 11 (2.19%) cases of in hospital mortality, 6 (54.54%) were under ventilatory supports. Patients who died even under ventilatory supports was probably due to serious conditions and other comorbidities.

CONCLUSION

In this study, most patients with AE of COPD required ventilatory support (either non-invasive ventilation or invasive ventilation). Over half of patients were

discharged after making full recovery while some patients went on to receive long-term oxygen therapy. The mortality rate was low. This information is useful for peripheral hospitals in developing countries, as many lack ICU facilities and ventilatory supports.

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Anaesthetic Management for Whole Lung Lavage in Pulmonary Alveolar Proteinosis: A Case Report

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ABSTRACT

Pulmonary alveolar proteinosis is a rare disease in which lipoproteineous materials are deposited in the alveoli leading to impaired gas exchange and progressive hypoxaemia. Whole lung lavage is the treatment of choice. However, anaesthetic challenges like hypoxaemia, hypercarbia, hypotension during the procedure are always to be managed meticulously. Here, we describe a challenging case that underwent three sessions of whole lung lavage under general anaesthesia with endotracheal intubation with double lumen tube and one lung ventilation resulting clinical improvement in subsequent sessions.

KEY WORDS: *anaesthesia, lung lavage, pulmonary alveolar proteinosis*

INTRODUCTION

Pulmonary alveolar proteionosis (PAP) is a rare disease where the alveoli are filled with the lipoprotein secretions, impairing the normal gaseous exchange[1]. The progressive disease causes hypoxemia and severe respiratory failure. The etiology can be autoimmune, occupational or genetic defect. The secreted pulmonary surfactants are not cleared off the lungs due to dysfunctional granulocyte macrophages colony stimulating factor (GM-CSF). The whole lung lavage in PAP possesses anaesthetic challenges regarding oxygenation and ventilation due to the disease progression and existing hypoxaemia. This case underwent three sessions of whole lung lavage (WLL) under general anesthesia with improvement in oxygenation.

CASE

A 30-year lady was admitted in the pulmonary intensive care unit for shortness of breath and progressive dyspnoea since three months Her pulse rate was 120 beats/min, blood pressure 120/88mmHg, respiratory rate 26/min, afebrile and oxygen saturation 90% on 10 litres/min of oxygen via face mask with reservoir bag. Her room air oxygen saturation was below 70%. There were bilateral diffuse crepitations on chest auscultation. Her complete blood counts, platelets, renal function and liver function tests, blood glucose were within normal range. Her chest X-ray showed bilateral diffuse opacities. CT chest showed bilateral diffuse and widespread ground glass opacities with superimposed interlobular septal thickening giving "crazy paving pattern" appearance suggestive of PAP. The GM-CSF Antibody concentration was high which was suggestive of PAP. The whole lung lavage was planned under general anaesthesia. Her preoperative arterial blood gas (ABG) was PH-7.45, PaO_2-60mmHg, $PaCO_2$-42mmHg, FiO2-90%, HCO_3-24mmHg with high A-a gradient (>400mmHg).

Intravenous access was opened with 18G cannula. The routine ASA standard monitors: ECG, Noninvasive blood pressure, Pulseoximeter, capnograghy, temperature along with invasive arterial line in left radial artery and urinary catheter were placed. Preoxygenation was done with 100% oxygen and CPAP 10cmH2O for 5min in propped up position. She was induced with fentanyl 100mcg, titrating dose of Propofol 100mg and

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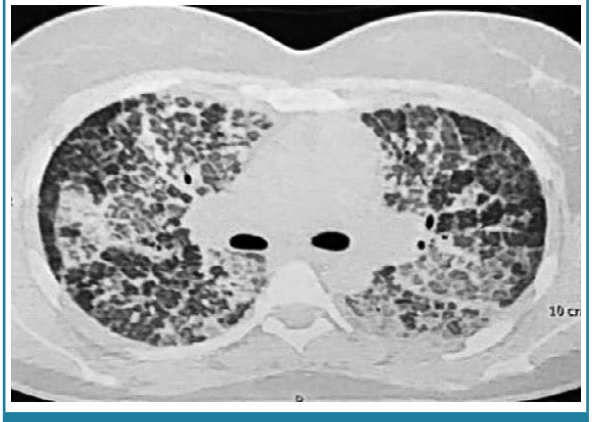
succinylcholine 100mg. Endotracheal intubation with double lumen tube (DLT) 35Fr left side was confirmed by auscultation and flexible pediatric bronchoscope. Anesthesia was maintained with sevoflurane, 100%oxygen and pressure control ventilation. Left sided whole lung lavage was performed. One litre of normal saline was infused in first cycle followed by five minutes of chest physiotherapy (percussion) and the saline was drained out. The position was maintained as head up and left lateral tilt during saline instillation to prevent spillage in right lung and trendelenburg, left lateral tilt during drainage out. Ten cycles of the lung wash was performed with around six litres of normal saline till milky effluent drained fluid was more clear. It took two hours and 40 minutes with positive balance of 340ml and urine output of 500ml. During the procedure, there were episodes of desaturation down to 70% which was managed with both lung ventilation, PEEP, 100% oxygen and manual bagging and saturation maintained at 85 -90%. Lung compliance, peak airway and plateau pressures were also monitored. At the end of the procedure, DLT was exchanged with the single lumen tube with subglottic suction size 7 mmID and lung recruitment was done. Inj Furosemide 20mg was given. Patient was kept in mechanical ventilation in airway pressure release ventilation mode with muscle relaxant and fentanyl sedation. Postoperative ABG and chest X-ray were sent. She was extubated next day and could maintain oxygen saturation of 90-92% with FiO2 of 0.9 which could be tapered to 0.6 after two days.

The second session of the left WLL was done after 2 weeks. Total 14 litres of normal saline wash was performed in 14 cycles with around positive balance of 1700ml, urine output 1400ml over a period of three hours. The oxygen saturation was maintained between 88%- 95%.She was extubated next day and maintaining saturation of 96% with FiO2 of 0.4.

After six weeks, the third lavage was performed in right lung with 10 litres of normal saline in 10 cycles. Her preoperative ABG was PH 7.45, PaO_2 47mmHg, $PaCO_2$ 40mmHg, $HCO_3$29mmHg, SaO_2 92%, A-a gradient 47mmHg in FiO2 0.24.Oxygen saturation was maintained at 90-95% with stable hemodynamics. Confirmation of no air leak in left lung was performed by ensuring no air bubble from left lumen of DLT during the ventilation of right side before the procedure. Postprocedure mechanical ventilation in PCV mode with single lumen tube was continued and extubated the next day. She was more comfortable than previous lavages and maintaining saturation 98%in FiO2 of 0.4 tapered to 0.24. She was discharged home after one week.

Picture1: Milky effluent fluid becoming more clear in subsequent lavages shown in numbered bottles



Picture 2: CT scan of pulmonary alveolar proteionosis showing opacities "crazy paving pattern"

DISCUSSION

The whole lung lavage is the main treatment for PAP.[2] It was first described by Juan Ramirez Rivera[3]. Hypoxaemia, hypercarbia, fever, difficulties with one lung ventilation, unstable hemodynamics, contralateral fluid leakage, pneumothorax are some of the complications challenging the anesthesiologists[4,5]. In this case, the anaesthetic challenges were intraoperative desaturation, hypercarbia, reduce compliance with high airway pressure and hypotension in the first session. Desaturation was managed by both lung ventilation with 100%oxygen and applying PEEP. CPAP preoxygenation done in this case was helpful to maintain oxygenation saturation during induction. Application of CPAP in lavage lung during

drainage is another option for hypoxemia prevention during the procedure. In the next sessions, there was hypercarbia which was successfully managed with the post procedure mechanical ventilation. Regarding the anaesthetic procedure, general anaesthesia was preferred as in other case reports also[6,7]. Total Intravenous agent (TIVA) or inhalational agent was used for the maintainence of anaesthesia in the literatures[8]. TIVA preserves hypoxic pulmonary vasoconstriction. Left sided DLT is preferred to avoid the difficulties of Right sided tube. In this case also, left sided tube was kept. The temperature was maintained with the warm normal saline for wash and forced air warming blanket covering the patient. There were episodes of desaturations during drainage phase and improvement of saturation during saline infusion due to the decrease in shunt fraction during instillation of fluid and increase in shunt fraction during the drainage phase.

Semi lateral position was done in this case. The dependent lung was lavaged to prevent the flooding of the ventilated lung. Lateral, semi lateral and supine, all the positions have been mentioned in the literature[9,10]. The most infected lung is lavage first but in case both the lungs are affected, left lung is lavaged first as also done in this case. However, there is always risk of spillage of fluid in the ventilated lung causing increased airway pressure, ventilation perfusion mismatch and hypercarbia. The first lavage was challenging as patient was severe hypoxemic further complicated by spillage on ventilated lung which could be successfully managed in this case. In subsequent sessions, she has gradual clinical and functional improvement.

The multidisciplinary approach between the anesthesiologists, pulmonologists, intensivists and the respiratory therapists with team spirit is required for the successful management of the PAP.

DECLARATION:

The patient has given written informed consent for publication in a scientific journal and has been informed that the direct identity will not be disclosed. However, complete anonymity cannot be guaranteed as it is possible somebody (caregiver or relative/ friend) may recognize the patient from the information published in the journal.

Conflict of Interest: None

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