SINGLE SETTING ERCP AND LAPAROSCOPIC CHOLECYSTECTOMY IS A SAFE PROCEDURE IN PATIENTS WITH CHOLECYSTO-CHOLEDODCHOLITHIASIS: A PROSPECTIVE STUDY IN A PERIPHERAL-LEVEL HOSPITAL

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ABSTRACT

The ideal management of cholecysto-choledocholithiasis is an open cholecystectomy (OC) with the common bile duct (CBD) exploration worldwide. The single setting 2-stage approach- endoscopic retrograde cholangiopancreatography (ERCP), endoscopic sphincterotomy (EST), and CBD clearance followed by laparoscopic cholecystectomy (LC) offers an advantage, mainly by reducing the hospital stay, the cost, and the morbidity. The Objective of the study is to compare the ERCP+LC single setting approach with an OC+CBD exploration for the treatment of cholecysto-choledocholithiasis. This is an interim analysis of 160 patients with 83 (51.9%) patients in ERCP+LC and 77 (48.1%) in an open procedure (OC+CBD exploration) group respectively. We did a prospective study in patients admitted for the management of the cholecysto-choledocholithiasis in the Department of Surgery at the Lumbini Medical College and Teaching Hospital from November 2012–October 2015. They underwent 2-stage ERCP+LC in a single setting and we compared them with 2-stage OC+CBD exploration in a single setting approach. The patients with the open procedure were our control group. All the included cases in the study were elective. The procedure was feasible in our hospital. Similarly, the hospital stay was significantly shorter in the ERCP+LC group; 3.92±0.719 days vs 10.30±1.557 days, p <0.05. There was a significant difference in the total morbidity of ERCP+LC group 7 (8.4%) vs 14 (18.2%), p <0.05. Here, wound infection in the ERCP+LC group was 2 (2.4%) vs 4 (5.2%) and there was one case of abdominal collection 1 (1.2%) which was managed symptomatically. The incidence of retained CBD stone in the ERCP+LC was 3 (1.2%) which was managed successfully with ERCP. In all the cases, post-ERCP amylase value was found to be within the normal limit. The result of our study suggests, single setting ERCP+LC at the peripheral-level hospital is feasible in terms of cost, length of hospital stay, morbidity and stone clearance.

KEYWORDS

Common bile duct stones, Endoscopic Retrograde Cholangiopancreatography, Laparoscopic Cholecystectomy Open Cholecystectomy

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**INTRODUCTION**

Choledocholithiasis is the cause of significant morbidity and mortality due to its complications in the form of gallstone pancreatitis, obstructive jaundice, and cholangitis. The incidence ranges from 5 to 15% and up to 20% in the elderly population.1 And, up to 25% of cases, CBD stones are discovered intraoperatively.2 The primary imaging modalities like Transabdominal USG has the sensitivity of 73% and specificity of 91%.3 Similarly, MRCP has the sensitivity of 81-100% and specificity of 92-100% whereas, ERCP/EUS has 88-97% and 96-100%.4-6 These imaging modalities can detect CBD stones as well as dilated biliary ductal system. Other modalities available are Liver function test (LFT),3 intraoperative laparoscopic ultrasonography and helical CT cholangiography.4-6

Laparoscopic cholecystectomy with or without intraoperative cholangiogram (IOC) is the current gold standard for the treatment of acute or chronic cholecystitis.7-9 There is no single method or algorithm that is superior to others when it comes in the treatment of the obstructive complication of calculus biliary diseases like jaundice, pancreatitis, cholangitis, and asymptomatic choledocholithiasis.8,10 There has been a drastic transformation in the management of CBD stones after the introduction of ERCP in 1968.11 Recently, Aleknaite et al.12 showed that ERCP has a better diagnostic performance than IOC. Traditionally, the treatment involves what is known as a two-setting procedure, that consists of preoperative ERCP followed by LC. Alternatively, LC with IOC and intraoperative CBD exploration or ERCP performed at a later date in the traditional two-step framework.13 A recent systemic review and meta-analysis recommended ERCP followed by LC rather than ERCP followed by the wait and watch. Even though two groups had no differences in mortality, results showed that LC after ERCP could be done safely including high risk patients.14,15

In the United States nationwide assessment for the treatment of CBD stone showed drastic increase in the use of ERCP+LC from 52.8% to 85.7% (p<0.001) and decrease in the trend of open CBDE (30.6% vs 5.5%; p<0.001) and laparoscopic CBDE (9.2% vs 3.0%; p<0.001).16 Safety and efficacy of single setting ERCP+LC were shown in the RCT done by Cuschieri et al.17 long back. Where they found that with the proper selection of the patients, ERCP+LC leads to the better management of patients with CBD stones. Here, in our study both the procedures (ERCP+LC) had been done in a single setting by a single team at the peripheral-level hospital. And thus the primary objective of this study is to check the feasibility of the procedure, whereas secondary objectives are to (1) detect the morbidity (cholangitis, pancreatitis, abdominal collection and wound infection), (2) the length of hospital stay, and (3) stone clearance, respectively. The new thing about this study is that all of these procedures ERCP and LC were performed at the single setting by the same surgeon who was trained for the ERCP, LC and open procedure, respectively.

**MATERIALS AND METHODS**

This was a prospective study done on patients admitted for management of the cholecysto-choledocholithiasis in the Department of Surgery at the Lumbini Medical College and Teaching Hospital from November 2012–October 2015. The patients were followed up for 1 year after the surgery. This is a peripheral setting hospital located in a remote city of Nepal-“Palpa”. The study was approved by the institutional ethical committee-“IRB of Lumbini Medical College and Teaching Hospital” and written consent was obtained from all of the patients. This study had been registered at ClinicalTrials.gov- NCT04213092. A comprehensive literature search published in English was done till 2019 using Hinari, PubMed, Cochrane Library, EMBASE, Web of Science, and ScienceDirect.

<table>
<thead>
<tr>
<th>SN.</th>
<th>Inclusion criteria</th>
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<th>Exclusion criteria</th>
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<tr>
<td>1.</td>
<td>All the sonological proven cases of choledocholithiasis with cholelithiasis</td>
<td>1.</td>
<td>Clinical, radiologic, or biochemical evidence of cholangitis and pancreatitis.</td>
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<tr>
<td>2.</td>
<td>CBD diameter &lt;2cm.</td>
<td>2.</td>
<td>Evidence of cirrhosis, intrahepatic gallbladder, liver mass or abscess, neoplasm, Suppurative or necrotizing cholecystitis, gall bladder empyema, or perforation, Pregnancy.</td>
</tr>
<tr>
<td>3.</td>
<td>Age &gt;13 yrs.</td>
<td>3.</td>
<td>Age &gt;85 yrs.</td>
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Table 2: The inclusion and exclusion criteria's for open cholecystectomy and CBD explorations.

<table>
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<th>Criteria for Open cholecystectomy and CBD exploration</th>
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<tr>
<td><strong>SN.</strong></td>
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<tr>
<td>1.</td>
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<td>2.</td>
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<td>3.</td>
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This is an interim analysis of 160 patients with 83 (51.9%) patients in ERCP+LC and 77 (48.1%) in open procedure (OC with CBD exploration) group respectively. The primary objective was to compare the single setting ERCP+LC with OC+CBD exploration and the secondary objectives were to study (1) the feasibility of the procedure, (2) detect the morbidity (cholangitis, pancreatitis, abdominal collection, and wound infection), (3) the length of stay, and (4) the stone clearance, respectively. We defined our single-setting procedure as ERCP followed by LC. The patients from an open procedure group were those who underwent the procedure before our team was trained to carry out the ERCP. This open procedure group also included 10 patients who underwent open surgery due to unsuccessful ERCP. And finally, we compared ERCP+LC group with those who underwent the open procedure. The inclusion and exclusion criteria’s for ERCP+LC and open procedure are shown in Table 1 and Table 2, respectively.

After being informed about the related therapeutic maneuver, the patients were chosen for the sequence of endoscopic procedure and LC. And, the unsuccessful patients underwent through the OC with CBD exploration along with choledochoscopy. General anesthesia with nasal endotracheal intubation was done in all the patients. Antibiotic prophylaxis was given according to the standard recommendation for cholecystectomy. The ERCP procedure was performed with the patients in the prone position. A duodenoscope (TJF160R, Fujinon, Japan) was inserted into the second segment of duodenum via the mouth. A cholangiogram was carried out using C-arm X-ray (SIEMENS) and an EST was performed to extract the CBD stones. The stones were removed by basket or balloon catheter. Stones larger than 10 mm were removed using a mechanical lithotripter. Following ERCP, care was taken to remove all the gas from the stomach to facilitate LC. The patients were then placed in the reverse Trendelenburg position. LC was performed using the four trocar technique. A sub-hepatic drain was positioned if there was any concern about the possible bile leakage or bleeding in the postoperative period.

In cases of failed ERCP, the patients were placed in the supine position and OC with CBD explorations were performed at the same setting. A right subcostal incision was given for the open surgery. Cholecystectomy was performed ante-grade or retro-grade technique depending upon the anatomical variations of the gallbladder. CBD was opened below the opening of the cystic duct and stone clearances were done. To assure the stone clearances intraoperative choledochoscopies were performed. All the procedure viz. ERCP, LC, and open surgeries were performed by an experienced single surgeon and his team.

The statistical data were analyzed with a t-test, Pearson’s χ², Fisher’s exact test, Mann Whitney’s test, and Kruskal Wallis test using a statistical analysis program (SPSS 16), p <0.05 was considered statistically significant.

**RESULTS**

**Patient Characteristics:** In total 160 patients were included for the study. Where 83 (51.9%) patients in (ERCP+LC) group met the criteria out of 93 (58.1%) patients. And, 10 (6.2%) out of 93 were converted to open procedure and were included in the total number of the open procedure (the control group). The total number of open procedures were 77 (48.1%). Out of ten, 2 (2.1%) had difficult cannulation due to the edematous duodenal wall, 3 (3.2%) had bleeding from the ampullary site and in 5 (5.4%) patients stone was large and we were unable to break it due to its hardness.

The age range was between 13 years to 76 years, with the mean age of 44.2±17.1 in the ERCP+LC group and 65±12.1 in the open CBD exploration group. The difference between the age of the patients between these two groups was found to be statistically significant. Here, those who
underwent the open procedure were older than the group of patients who underwent through successful ERCP+LC. This non-homogeneity in the age could be a subject to bias. And, when we consider the sex of the patient across the group, the total number of a male patient in the ERCP+LC group were 16 (19.3%) and female patients were 67 (80.7%), respectively. Whereas, the total number of male patients in the open group were 14 (18.2%) and female patients were 63 (81.8%) respectively. The difference between the male and female across the groups were statistically significant, \(p<0.005\) this means the females were found to have more incidences of gallstones in this study. Similarly, demographical and clinical characteristic showed the significant difference between the male and female patients \((p<0.05)\), since the diagnosis understudy was commonly seen in female patients.

**Comparison between ERCP+LC and the open group:** When analyzing the data, the size of the CBD in ERCP+LC group was 9.7±1.7mm and in OC+CBD exploration group was 23.5±2.2mm respectively. The difference was statistically significant \((p<0.05)\). Whereas, total leucocyte counts (TLC), level of preoperative bilirubin, liver transaminase levels and alkaline phosphatase were statistically not significant \((p>0.05)\) as compared to the conversion to open procedure as shown in and Table 4 and Fig. 1 and 2. Also, the infectious complication in ERCP+LC group was found to be less than OC+CBD group \((18.2\% \text{ vs } 8.5\%), \ p<0.05\) Fig. 1 and 2 and Table 3.

The mean duration of surgery for ERCP+LC and OC+CBD exploration were 82.2±11.1 and 124.7±10.2 minutes respectively and were statistically significant \((p<0.05)\). The serum amylase in the postoperative period was not significantly associated with the type of procedure \((p>0.05)\). Whereas, postoperative complications were significant in the case of open procedure in the form of minor wound infection and fever \((p<0.05)\). Similarly, the mean number of the postoperative days of stay was 3.9±0.7 in ERCP+LC

<table>
<thead>
<tr>
<th>Complications</th>
<th>ERCP+LC</th>
<th>OC+CBD Exploration</th>
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<tbody>
<tr>
<td>Fever</td>
<td>4 (4.8%)</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>2 (2.4%)</td>
<td>4 (5.2%)</td>
</tr>
<tr>
<td>Abdominal collection +fever + TLC</td>
<td>1 (1.2%)</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>7 (8.4%)</td>
<td>14 (18.2%)</td>
</tr>
<tr>
<td>(p)-value</td>
<td>&lt;0.05</td>
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<table>
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<tr>
<th>Parameters</th>
<th>ERCP+LC</th>
<th>OC+CBD</th>
<th>(P)-value</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>44.2±517.1</td>
<td>65±12.1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (19.3%)</td>
<td>14 (18.2%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Female</td>
<td>67 (80.7%)</td>
<td>63 (81.8%)</td>
<td></td>
</tr>
<tr>
<td>CBD size</td>
<td>9.67±1.7mm</td>
<td>23.5±2.2mm</td>
<td>&lt;0.05</td>
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<tr>
<td>LFT (Liver function test)</td>
<td>Non-significant</td>
<td>Non-significant</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Serum amylase rise in post-operative period</td>
<td>Non-significant</td>
<td>Non-significant</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Duration of Ssurgery</td>
<td>82.2±11.1 mins</td>
<td>124.7±10.2 mins</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Length of stay</td>
<td>3.9±0.7 days</td>
<td>10.3±1.5 days</td>
<td>&lt;0.05</td>
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<tr>
<td>Follow up incidence of retained stone in 3 months</td>
<td>3 (1.2%)</td>
<td>none</td>
<td>&gt;0.05</td>
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group and 10.3±1.5 days in OC+CBD exploration group respectively. And, it was statistically significant \((p<0.05)\) as shown in Table 3 and 4 and Fig. 1 and 2.

The stone clearance rate was 100% in the open group at 3 months follow up as compared to the ERCP+LC group which was 96.3%. The USG findings were abnormal in the form of prominent CBD but without stones in the OC+CBD exploration group. Whereas, there were 3 cases of (3.6%) of retained stones in ERCP+LAP cholecystectomy group and were successfully managed with ERCP. The patients were also followed up with LFT who had prominent CBD and were found to be within normal limits. And, the incidence of retained stones between these groups was not statistically significant \((p>0.05)\).

**DISCUSSION**

The most common cause for obstructive jaundice and recurrent cholangitis are due to the CBD stones. And, most of the CBD stones are secondary
as only 15% of the cases are primary CBD stones. These can cause significant morbidity and mortality, thus these patients need to be adequately evaluated before the surgery. To provide comprehensive treatment to these patients, biliary surgeons must master more than one techniques in the current era. The endoscopic procedures have made a significant impact on the treatment of gallstone diseases in the last 3 decades. But their diagnostic usefulness has been taken over by other non-invasive modalities in the management of benign biliary diseases.

Novel techniques like LC-LCBD (laparoscopic cholecystectomy-laparoscopic bile duct exploration), LC-EST and laparoscopic-endoscopic rendezvous (LREV) have shown exciting results. However, a recent meta-analysis from Cochrane Library failed to determine the effect of LREV vs ERCP on morbidity and mortality. Similarly, other modalities like laparoscopic Transcystic (TC) and Transductal (TD) has emerged for the extraction of CBD stones. These study showed that TC and ERCP/EST has similar results compared to the TD approach. A systemic review failed to show a significant difference in the morbidity, mortality, retained stones, and failure rate between LCBD and ERCP. Yet, a recent meta-analysis showed that LCBDE+LC is superior to ERCP+LC for GB stone and CBD stone in terms of perioperative safety as well as short and long-term postoperative efficacy. These revolutionary techniques need specialized facilities with trained personnel. The argument against and for the laparoscopic CBD exploration is related to the patient's factor viz. the diameter of CBD <8mm, multiple stones/distal impaction, cost, and duration of the anesthesia and the feasibility related factor in the remote center respectively. Moreover, when two procedures are performed by the two separate teams at the same time, it may lead to technical difficulties. But, in our study this difficulty was overcome as both the procedures were performed by the same team with experience in these procedures at the peripheral-level hospital. And, we compared ERCP+LC with OC+CBD exploration in a single-setting by a single team.

In our study, the success rate of stone clearance was 89.2% (83 out of 93) which is comparable to a study done by Koc et al where they reported the success rate of stone clearance of 94.4%. In their series, 5.5% of patients required multiple ERCP interventions, for retained stones but in our series, we immediately operated the patient with the intraoperative cholecystoscopy and CBD exploration at the same setting with the success rate of 100%. We justify our approach of conversion in case of difficulties and the patients were preoperatively counseled regarding the procedure. As our experience was of the peripheral-level hospital, it was very difficult to convince the patients to undergo through the second ERCP procedure. Also, failure of the ERCP was not due to the technical error rather it was due to the high burden of stones, the size (>2.5cm) and impaction of the stone at the distal end of the CBD. Thus, in our scenario laparoscopic CBD exploration was not an option and our open approach in those 10 cases were understandable. Our result is better than a study done by Cinar et al where conversion to open cholecystectomy was 11.3% following single ERCP and 29.2% following two or more ERCP respectively. ERCP+LC related complications were 7 (8.4%) in our study and it includes only minor complications. But, one of the cases had intra-abdominal collection post-surgery and it was managed symptomatically. If we observe the types of complications we encountered, no patients in our study had evidence of pancreatitis and cholangitis following the procedure. However, the milder complications that we encountered, were tackled in the OPD basis. This gives our study a new thought that it can be done at the peripheral setting very safely, where we do not have the luxury of an experienced gastroenterologist who is going to help during the procedure and/or in the follow-up procedure.

Our result is comparable to other series where ERCP-associated complication rate was 11.1%. Whereas, complication rates in our open group was 14 (18.2%) which were minor complications like fever and wound infections. And, they were successfully managed with symptomatic treatment. Tzovaras et al noted a significant decrease in the length of hospital stay and postoperative serum amylase values by using a novel single-setting procedure LREV technique. Rábago et al also compared a single setting to a double setting approach. The group receiving the single-setting approach with intraoperative ERCP exhibited a decrease in morbidity in addition to the shorter hospital stay and decreased hospital costs. The decrement in morbidity these group resulted from the lower rate of papillotomy and lower rates of post-ERCP pancreatitis. By limiting the number of operative procedures, patients can be safely and more efficiently treated using this method. The single setting technique of ERCP and LC is simply such a novel procedure at our institution that, it would be challenging to achieve this increased statistical power at other institutions of Nepal. These data for an example identifies a 3.7% rate of retained stone after ERCP. Anecdotally, the overall retained stone rate is around the vicinity of 5%. The retained stone rate in some series has been documented to be as high as 12% and as low as 2–4% as in our series.
The success of ERCP in our series is comparable to the study of Zang et al. The parameters like the stone clearance rate from the CBD, the duration of surgery, and the length of hospital stay were similar in both of the studies.

With regards to same setting surgery for patients with concomitant gallstones and choledocholithiasis, LCBDE is another good option that avoids duodenoscopy and LC. And the debate has been ongoing since long about the better method of management. Multiple RCTs showed that both of the methods viz. LCBDE+LC and ERCP+LC are equally effective in the diagnosis and the treatment of CBD stones. An Up-to-date meta-analysis also showed that LCBDE+LC is superior to pre-EST+LC. According to European Society of Gastrointestinal Endoscopy (ESGE) guideline, ERCP (with EPBD rather than EST) should be done in CBD stones <8mm in size. Whereas, the ERCP may not be appropriate for the stone size of >25mm without a laser lithotriptor. And LCBDE or open CBD with IOC would be a better option for larger stones and residual stones. However, LCBDE is limited to centers with appropriate expertise. A recent meta-analysis reported that intra-operative ERCP is superior to pre-operative ERCP in terms of exposure to anesthetic agents, higher incidence of pancreatitis, longer hospital stay and cost. Retrospective study of single setting approach done by Jones et al. showed that both LC+IOC then ERCP also showed a significant reduction in the cost and time for the treatment of CBD stones. They also found that ERCP was better than MRCP or LCBDE in terms of cost and time.

Fujimoto et al. found pneumobilia as a significant risk factor for cholecystitis and recurrent CBD stones following the endoscopic procedure. They also noted that 53.8% of the patients developed GB cancer following the procedure but long-term evidence is lacking regarding the delayed effects of papillotomy. Also, Elgeidie et al. showed that both LC with intraoperative endoscopic sphincterotomy (IOES) and LC with laparoscopic CBD exploration (LCBDE) were minimally invasive and effective treatments that can be done safely for the management of cholecysto-choledocholithiasis. And they preferred LC-IOES provided the hospital has facilities with the experienced personnel. And a recent meta-analysis by Tang et al. also supports this method. If we do LCBDE for larger stone with the laser lithotripsy then again the issues related to T-tube drainage will add on to the prolonged morbidity to the patient. Besides, if the stone clearance was not successful then open procedure has to be carried out for clearance of the stones. Finally, this justifies our approach at the peripheral-level hospital for the management of patients with cholecysto-choledocholithiasis.

Table 5 summarizes and compares our study with a meta-analysis of one- vs. two-stage laparoscopic/endoscopic management of CBD stones.

The main strength of our study: It is a single setting procedure done by a single team and thus it is a revolutionary concept which is pragmatic with a 100% success rate as in our case. Therefore the results are applicable generally, not just to centers with specialized expertise but also at the peripheral centers. The burden of central referral, as well as the waiting period for both the procedures, was decreased in our study. This also led to the reduction in the duration of anesthesia, the length of hospital stay, the complications following the procedure and the financial burden respectively. Similarly, in case of rare complications of ERCP like bowel perforation and intra procedure bleeding, they can be tackled at the same setting by the open procedure.

The limitation of our study: It is a single center study with limited number of patients (n=160) and two groups of patients were found to be inhomogeneous concerning to age and this makes it difficult to establish a clear consensus regarding larger stones in open group. Similarly, in cases of failed ERCP, multiple attempts of ERCP at the different interval were not consented due to geographic and economic condition.

In conclusion, endoscopic stone extraction and LC performed in the same setting is feasible and is safe in patients with gallstones and concomitant CBD stones. We propose that surgeons at the peripheral-level hospital experienced in both the procedures may attempt this procedure. This will reduce the total cost, time, referral and the morbidity of undergoing procedures in a higher setting as it is very safe and feasible according to our results.

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The authors' responsibilities were as follows: NP and GK are the first authors. NP designed, and conducted the research. NP and GK were responsible for the data collection, analysis, interpretation, and drafting. And final approval of the manuscript was given by both the authors. The authors have no conflicts of interest to declare.

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