Endoscopic retrograde cholangiopancreatography versus conservative treatment for patients with symptomatic small common bile duct stones: A randomized controlled trial

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Abstract

Background: Endoscopic retrograde cholangiopancreatography (ERCP) is the recommended treatment for common bile duct stones (CBDS). However, CBDS, tiny ones, can spontaneously pass through the ampulla of Vater, reducing unnecessary ERCP and its related significant complications.

Objectives: This study compared endoscopic stone extraction versus conservative treatment for managing symptomatic small CBDS.

Patients and methods: This randomized controlled trial included 168 patients with symptomatic CBDS (≤ 7 mm) and gallbladder stones. Of these, 85 patients underwent endoscopic stone extraction, and 83 patients underwent conservative treatment for the CBDS, followed by laparoscopic cholecystectomy and intraoperative cholangiography between June 2019 and March 2023. The primary outcome was the overall success rate, while useless procedures, morbidity, mortality, length of hospital stay, total cost, and recurrent biliary symptoms were considered secondary outcomes.

Results: Our study showed that the ERCP group had a significantly higher overall success rate (96.5% vs. 22.9%, P < 0.001), fewer useless procedures (14.1% vs. 77.1%, P < 0.001), a shorter median hospital stay (5 vs. 8 days, P < 0.001), and reduced total costs (1810 vs. 2250 US$, P < 0.001). Both groups had no significant difference in morbidity or recurrent biliary symptoms (2.4% vs. 7.2%, *P* = 0.14). There was no mortality rate in both groups.

Conclusion: Symptomatic small CBDS should be managed surgically as early as possible. Endoscopic stone extraction has a significantly high success rate, a shorter hospital stay, and a lower total cost. The conservative treatment for symptomatic small CBDS is useless and should not be practiced.

Keywords: Endoscopic retrograde cholangiopancreatography, conservative treatment, spontaneous passage, small common bile duct stone

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Introduction

Common bile duct stones (CBDS) might cause severe morbidity, such as biliary colic, obstructive jaundice, ascending cholangitis, biliary pancreatitis, liver abscess, or a combination **(European Association for the Study of the Liver, 2016)**. Therefore, the guidelines recommend CBDS extraction regardless of size, number, and clinical symptoms to avoid these severe complications if the patients can tolerate surgical treatment **(Buxbaum et al., 2019; Manes et al., 2019)**.

Endoscopic stone extraction by endoscopic retrograde cholangiopancreatography (ERCP) is the recommended option for managing CBDS **(European Association for the Study of the Liver, 2016)**. ERCP is a highly effective procedure with a success rate of 85% to 95% **(Samardzic et al., 2010)**. Nevertheless, it is essential to note that ERCP is associated with a significant level of risk, ranging from 5% to 15%. It can result in severe short-term and long-term complications, such as pancreatitis, cholangitis, post-sphincterotomy bleeding, retroperitoneal perforation, recurrent CBDS, cholangiocarcinoma, and anesthesia-related adverse events **(Reinders et al., 2011; Omar et al., 2015; Dumonceau et al., 2020; Johnson et al., 2020).**

Furthermore, ERCP may be a useless procedure in a significant proportion of cases (40-60%) due to the spontaneous passage of CBDS, failed cannulation, or retained stone **(Samardzic et al., 2010; Moller et al., 2014).** Therefore, ERCP should be avoided when the spontaneous passage of CBDS is suspected **(Khoury et al., 2019; Saito et al., 2023).**

On the contrary, some small studies reported a high and safe spontaneous migration of CBDS through the ampulla of Vater, recommending conservative care for CBDS **(Frossard et al., 2000; Collins et al., 2004; Gao et al., 2013; Lefemine and Morgan, 2011; Khoury et al., 2019).** The exact CBDS size that can be passed spontaneously through the papilla is unknown **(El Nakeeb et al., 2016).** Many papers **(Gao et al., 2013; Sanguanlosit et al., 2020; Saito et al., 2023)** reported that the spontaneous passage of CBDS was linked to a single CBDS smaller than 6 mm, a CBD that wasn't dilated (< 10 mm), asymptomatic patients, and long intervals between diagnosis and ERCP.

The management of small CBDS, especially in symptomatic patients, remains debatable **(Sharma et al., 2012; Sanguanlosit et al., 2020)** as the intervention and conservative treatment benefits and hazards remain under-evaluated **(Moller et al., 2014).** This study compared the efficacy of endoscopic stone extraction and conservative care for symptomatic small CBDS, followed by laparoscopic cholecystectomy (LC) and intraoperative cholangiogram (IOC) for gallbladder stones.

Patients and methods

Study design: This is an open label, randomized clinical trial with parallel groups. Group 1 was the endoscopic stone extraction, and Group 2 was the conservative treatment for CBDS. Our Institutional Ethics Committee approved this study. This trial followed the Declaration of Helsinki and the Consolidated Standards of Reporting Trials **(World Medical Association 2013).** All study participants gave written informed consent.

Study participants: This study included all patients who presented with symptomatic small CBDS and gallbladder stones between June 2019 and March 2023 at the endoscopy unit of Qena University Hospitals, Egypt. The inclusion criteria were patients diagnosed with symptomatic (biliary colic, obstructive jaundice, cholangitis, or pancreatitis) small CBDS (≤ 7 mm) and gallbladder stones, age 20-70 years, American

Society of Anesthesiologists scores of I-III (I: healthy patient, II: patient with mild systemic disease, and III: patient with severe systemic disease), and a serum bilirubin level ≤ 10 mg/dL. Patients with acute cholecystitis, severe cholangitis, severe pancreatitis, hepatobiliary malignancy, perforated gallbladder, biliary peritonitis, pregnancy, CBD stricture, previous sphincterotomy or cholecystectomy, or contraindications to ERCP or LC were excluded.

Sample size calculation and randomization: We calculated the sample size (https://clincalc.com/Stats/SampleSize.aspx) based on an estimated success rate of 52% in the ERCP group and 76% in the conservative group **(El Nakeeb et al., 2016)** with a power of 90% and a reliability of 0.05. We found that 82 patients were needed for each group. We added 5% for possible dropouts. Finally, according to a computer-generated random number, 172 eligible patients were randomly divided into two equal groups (Group 1: ERCP group and Group 2: conservative group). Out of the 86 patients assigned to each group, one patient was excluded from the ERCP group, while three were excluded from the conservative group. Therefore, the final analysis included 85 patients in the ERCP group and 83 patients in the conservative group **(Fig.1)**.

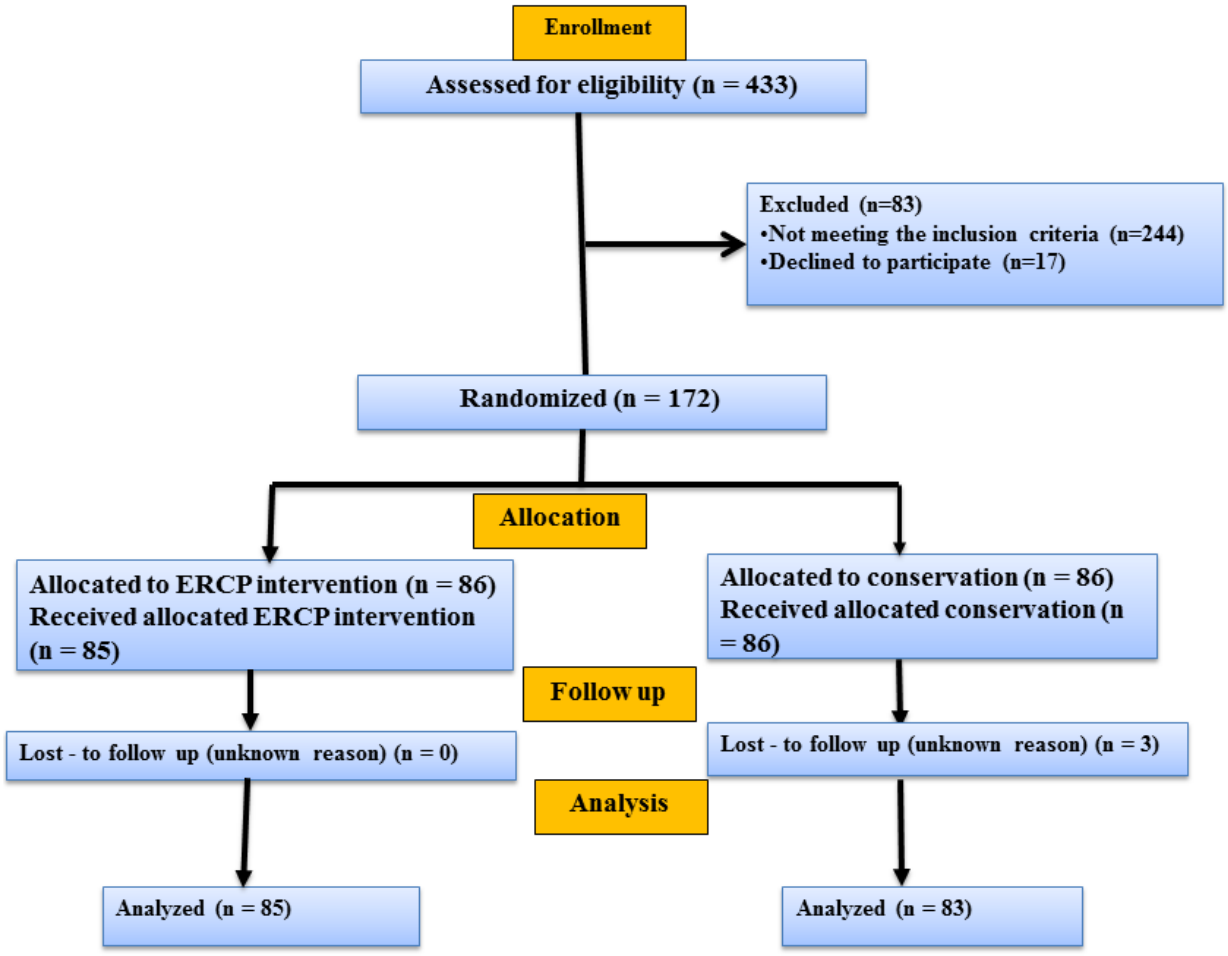

Fig.1. Consort flow diagram

Preoperative assessment: All patients underwent a careful history taken (biliary colic, jaundice, fever, or pancreatic pain), a physical exam, laboratory tests (bilirubin and alkaline phosphatase levels), and radiological tests (abdominal ultrasonography showing possible CBDS or dilated CBD > 7 mm). All suspected patients underwent magnetic resonance cholangiopancreatography (MRCP) to confirm CBD diameter, the number, and the largest size of CBDS. The stones was classified according to size into 3 classes; class I < 3 mm, class II = 4-5 mm, and class III = 6-7 mm. Computed tomography (CT) was done in selected cases. The blood test was repeated on the day of the LC.

ERCP group: ERCP performed as early as we could. All ERCP procedures were performed in the prone position under sedation or general anesthesia. Deep cannulation was attempted with a biliary cannula, a sphincterotome, or a precut needle. Limited sphincterotomy followed by papillary balloon dilation was performed to extract the CBDS using a retrieval balloon or basket catheter under fluoroscopic guidance. After biliary tract irrigation, a balloon occlusion cholangiogram was performed to ensure complete clearance of the CBD. A biliary drainage stent was inserted if indicated **(Figs 2A-D)**. LC followed the ERCP in the same hospital admission.

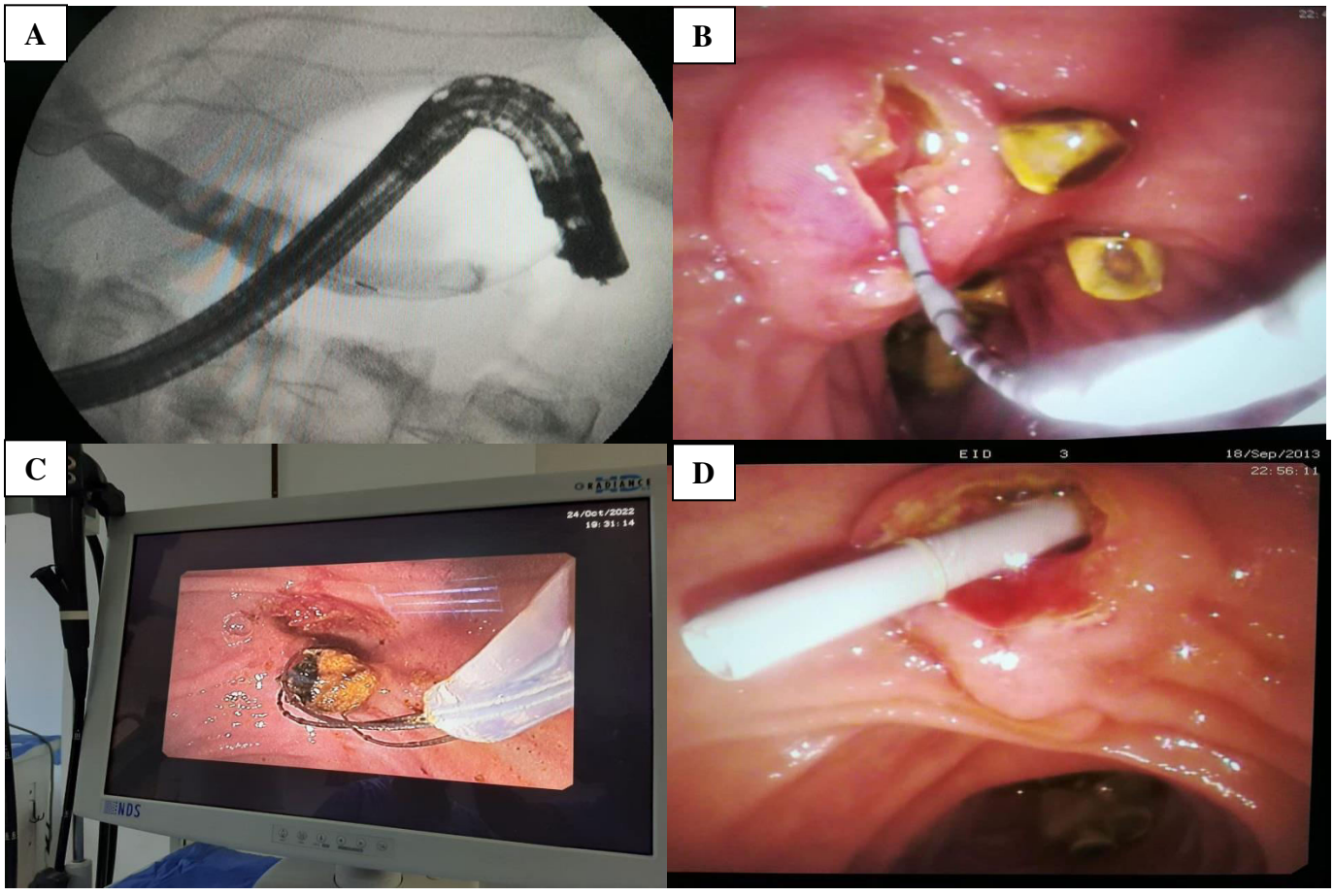

Fig.2. ERCP; A: ERCP shows multiple small CBDS; B: Balloon stone extraction; C: Basket stone extraction; D: CBD plastic stent

Conservative group: Patients received medical treatment in the form of antibiotics, analgesics, and antispasmodics for at least five days before LC and IOC.

LC and IOC: On the day of the operation, patients have a clinical and laboratory assessment (bilirubin level) to evaluate any potential improvement or deterioration in their condition. LC was performed according to the SAGES Safe Cholecystectomy Program. IOC was achieved through the cystic duct. If the IOC revealed CBDS, a trial of saline flushing, intraoperative ERCP, or LCBDE was tried. Failure of LC and performing an IOC cancel the procedure and convert to open surgery.

Follow-up: The patients were followed-up at the outpatient clinic at the end of the 1st week, 1st month, and then annually. The follow-up assessment included a clinical examination, bilirubin level, and abdominal ultrasound. MRCP was done when indicated. The patients were instructed to return if they complained of recurring symptoms or suspected adverse events at any time.

Outcomes: The primary outcome was the overall success rate, while useless procedures, morbidity, mortality, length of hospital stay, total cost, and recurrent biliary symptoms were considered secondary outcomes. Spontaneous migration is confirmed when no stones are found at the ERC or IOC **(Frossard et al., 2000).** Overall success was no retained CBDS at the IOC after the ERCP or conservative treatment. Procedure success was defined as the CBDS removed by ERCP or passed spontaneously in the ERCP or the conservative groups. ERCP was useless when it failed to find or extract sludge or CBDS, while conservative treatment was useless when sludge or CBDS was found in the IOC **(Andreozzi et al., 2022; Saito et al., 2023).** Morbidity was defined as any new adverse event developed after diagnosis until the 30th post-LC day. Retained CBDS are detected within two years, while recurrent CBDS are seen after two years of the IOC. Based on the results of the previous studies **(Frossard et al., 2000; Andreozzi et al., 2022; Saito et al., 2023)** of the upper limit of the confidence interval for the largest CBDS diameter with spontaneous migration, we considered a CBDS of 7 mm on the MRCP as the upper cutoff value for the CBDS size in the analysis.

Statistical analysis

Statistical Package for the Social Sciences (SPSS version 22) was used to analyze the data. Using the Shapiro-Wilk test, the data's normality was examined. Categorical data are represented as frequencies (n) and percentages (%) and analyzed using Pearson's chi-squared or Fisher's exact test. The independent sample t-test compared normally distributed data expressed as mean ± standard deviation (SD). The Mann-Whitney U test compared data with a non-normal distribution, presented as the median and interquartile range (Q1-Q3). A p-value of less than 0.05 was regarded as statistically significant.

Results

Of 433 patients evaluated for symptomatic small CBDS (≤ 7 mm) during the study period, 172 patients were included and classified into the ERCP and conservative groups. Our center is a tertiary referral center in Upper Egypt, which serve four governments with a population of about 7 million. Patient demographic data and clinical characteristics are shown in Table 1, with no significant differences between both groups **(Table 1).** The size of the largest stone was recorded in one of the following three categories: less than 3, 4 to 5, and 6 to 7 mm. 70% of CBDS were classified as being ≤ 5 mm.

Table 1. Demographics data and clinical characteristics

Variables	ERCP (n = 85)	Conservative (n = 83)	*P*-value
Age (years) [1]	46.93 ± 8.16	46.31 ± 7.99	0.87
Sex (Female) [2]	49 (57.6)	49 (59)	0.86
BMI (Kg/m^2) [1]	26.80 ± 2.36	26.98 ± 2.32	0.88
ASA score [2]			0.95
I	57 (67.1)	54 (65.1)	
II	18 (21.1)	18 (21.7)	
III	10 (11.8)	11 (13.2)	
Laboratory findings			
Bilirubin (mg/dL) [3]	7 (5-8)	6 (5-8)	0.91
Alkaline phosphatase (IU/L) [3]	209 (127-269)	183 (134-239)	0.72
CBD diameter [3]	9 (8-11)	10 (9-11)	0.33
CBDS number [2]			0.74
Single	39 (45.9)	36 (43.4)	
Multiple	46 (54.1)	47 (56.6)	
Size of the greatest CBDS (mm)[1]	4.35 ± 1.52	4.65 ± 1.53	0.21
CBDS size class (mm)[2]			
Class I < 3	27(31.8)	23 (27.7)	0.7
Class II = 4-5	37 (43.5)	35 (42.2)	
Class III = 6-7	21 (24.7)	25 (30.1)	
Preoperative diagnosis [2]			0.15
Obstructive jaundice	68 (80)	66 (79.5)	
Biliary colic	7 (8.2)	6 (7.2)	
Cholangitis	7 (8.2)	8 (9.6)	
Pancreatitis	3 (3.6)	3 (3.6)	
Preoperative imaging [2]			0.97
Ultrasonography	85 (100)	83 (100)	
MRCP	85 (100)	83 (100)	
CT	4 (4.7)	5 (6)	

ERCP: endoscopic retrograde cholangiopancreatography; BMI: body mass index; ASA: American Society of Anesthesiologists; CBD: common bile duct; CBDS: common bile duct stone; MRCP: magnetic resonance cholangiography; CT: computed tomography.
[1] mean ± SD; [2] no (%); [3] median (IQR1 – IQR3).

ERCP procedure characters are shown in Table 2. The median interval between the diagnosis and ERCP was two days. Cannulation was done successfully in 82 patients (96.5%) and failed in 3 patients (3.5%), two due to a small papilla and one due to an intradiverticular papilla. Deep biliary cannulation was achieved by standard sphincterotomy in 76 patients (89.4%) and precut sphincterotomy in 6 patients (7.1%). ERCP revealed at least one CBDS or sludge in 73 patients (85.9%) and was extracted successfully by balloon and Dormia basket. The ERCP procedure was useless in 12 patients (14.1%) due to the spontaneous passage of stones in 9 patients (10.6%) and failed cannulation in 3 patients (3.5%) **(Table 2).**

Table 2. ERCP group outcomes

Parameters	ERCP (n = 85)
The interval time between diagnosis and ERCP (days) [1]	2 (2-3)
Deep biliary cannulation [2]	
Successful	82 (96.5)
Failed	3 (3.5)
Technique of cannulation [2]	
Standard sphincterotomy	76 (89.4)
Precut sphincterotomy	6 (7.1)
ERC [2]	
CBDS	73 (85.9)
No CBDS (Passed spontaneously)	9 (10.6)
Successful CBD clearance [2]	73 (85.9)
Useless procedure [2]	12 (14.1)

ERCP: endoscopic retrograde cholangiopancreatography; ERC: endoscopic retrograde cholangiography
[1] median (IQR1 – IQR3), [2] no (%).

The ERCP group had a statistically significant shorter median interval between diagnosis and LC (4 vs. 7 days, $P < 0.001$). Thirty-five patients (42.2%) in the conservative group versus only six patients (7.1%) in the ERCP group were improved clinically and laboratory at the time of LC ($P < 0.001$). However, both groups had no significant difference in the median bilirubin level (7 vs. 7 mg/dl, P = 0.65). In the ERCP group, IOC revealed complete clearance of CBDS in 82 patients (96.5%) [in 73 patients (85.9%) by previous ERCP, and in 9 patients (10.6%) the stone passed spontaneously)], and in the remaining three patients (3.5%), the CBDS was removed by trans-cystic stone extraction. In the conservative group, IOC revealed complete clearance of CBDS in 19 patients (22.9%). In the remaining 64 patients (77.1%), the CBDS was removed by intraoperative ERCP (48 patients, 57.8%) and LCBDE [(trans-cystic in 11 patients (13.3%), and trans-choledochal in 5 patients (6%)]. Neither group had a statistically significant difference in conversion rate to open surgery **(Table 3).** Three patients were converted to open surgery due to dense adhesion of Calot's triangle with no significant difference between either group (1.2% vs. 2.4%, P = 0.56).

Table 3. Laparoscopic cholecystectomy outcomes

Parameters	ERCP (n = 85)	Conservative (n = 83)	*P*-value
The interval time between diagnosis and LC [1]	4 (3-4)	7 (6-7)	**0.001**
Improved patients [2]	6 (7.1)	35 (42.2)	**0.001**
Bilirubin (mg/dL) [1]	7 (6-8)	7 (5-9)	0.65
IOC [2]			**0.001**
CBDS	3 (3.5)	64 (77.1)	
No CBDS	82 (96.5)	19 (22.9)	
Management of CBDS [2]	3	64	**0.001**
Trans-cystic extraction	3 (3.5)	11 (13.3)	
Trans-choledochal extraction	0 (0)	5 (6)	
Intraoperative ERCP	0 (0)	48 (57.8)	
Conversion to open surgery [2]	1 (1.2)	2 (2.4)	0.56

LC: laparoscopic cholecystectomy; ERCP: endoscopic retrograde cholangiopancreatography; IOC: intraoperative cholangiogram; CBDS: common bile duct stone.
[1] median (IQR1 – IQR3), [2] no (%).Bold numbers indicate significance.

The overall success rate, irrespective of stone size, was significantly higher in the ERCP group (96.5% vs. 22.9%, $P < 0.001$). The ERCP group retrieved CBDS in 73 patients (85.9%), while the conservative treatment cleared CBD in 19 patients (22.9%). The ERCP procedure was useless in 12 patients (14.1%) [9 patients (10.6%), the stone passed spontaneously, and in 3 patients (3.5%), the stone was extracted laparoscopically]. Conversely, the conservative protocol was useless in 64 patients (77.1%) due to failed spontaneous passage. Eight patients developed complications in both groups with no significant difference (2.4% vs. 7.2%, $P = 0.14$). There was a significantly shorter median hospital stay (5 vs. 8 days, $P < 0.001$) and reduced cost (1810 vs. 2250 US$, $P < 0.001$) in the ERCP group. Both groups had no significant difference in morbidity and recurrent biliary symptoms (2.4% vs. 7.2%, $P = 0.14$). Eight patients developed recurrent biliary symptoms (2 patients in the ERCP group and 6 patients in the conservative group) due to retained and recurrent biliary stones, and all patients were managed with ERCP and stone extraction. There was no mortality in both group **(Table 4).**

Table 4. Primary and secondary outcomes

Parameters	**ERCP (n = 85)**	**Conservative (n = 83)**	***P*-value**
Success rate [1]			
Overall success rate	82 (96.5)	19 (22.9)	**0.001**
Procedure success rate	73 (85.9)	19 (22.9)	**0.001**
Useless procedure [1]	12 (14.1)	64 (77.1)	**0.001**
Morbidity [1]	2 (2.4)	6 (7.2)	0.14
Biliary colic	0	3	
Pancreatitis	1	1	
Cholangitis	0	2	
Perforation	0	0	
Bleeding	1	0	
Mortality [1]	0	0	. [a]
Hospital stay [2]	5 (5-6)	8 (7-8)	**0.001**
Total cost (US$) [2]	1810 (1750-1875)	2250 (2125-2310)	**0.001**
Recurrent biliary symptoms [1]	2 (2.4)	6 (7.2)	0.14
Retained CBDS	1	2	
Recurrent CBDS	1	4	

ERCP: endoscopic retrograde cholangiopancreatography; US$: American dollar; CBDS: common bile duct stone.
[1] no (%),[2] median (IQR1 – IQR3).
Bold numbers indicate significance.
[a] No statistics are computed because mortality was consistent.

The spontaneous CBDS passage was encountered in 28/168 patients (16.7%) in both groups. The spontaneous passage rate was directly related to stone size categories. The study revealed that the rate of spontaneous passage was significantly higher (52%) for sludge or common bile duct stones (CBDS) with a size less than 3 mm, in comparison to 3.2% and 0% for CBDS measuring 4-5 mm and 6-7 mm, respectively **(Table 5).**

Table 5. Success rate regarding the stone size category

Class	ERCP (n = 85)	Conservative (n = 83)	Total
I (CBDS size < 3 mm) [1]	8/27 (29.6)	18/23 (78.3) [a]	26/50 (52) [b]
II (CBDS size = 4 – 5 mm) [1]	1/37 (2.7)	1/25 (4)	2/62 (3.2)
III (CBDS size = 6 – 7 mm) [1]	0/21 (0)	0/35 (0)	0/56 (0)

ERCP: endoscopic retrograde cholangiopancreatography; CBDS: common bile duct stone.
[1] no (%), [a] $P < 0.001$ ERCP vs. Conservative group; [b] $P < 0.0001$ class I vs. class II & III

Discussion

The common bile duct stone is a significant biliary morbidity that necessitates surgical intervention, if patients are candidates for surgery **(European Association for the Study of the Liver, 2016; Buxbaum et al., 2019; Manes et al., 2019).** There is a lack of consensus on the optimal time for treating CBDS. Most surgeons and endoscopists recommend rapidly extracting symptomatic CBDS **(Williams et al., 2008),** which can be done surgically with open or laparoscopic CBD exploration or endoscopically with ERCP **(Katsinelos et al., 2014).**

LC-ERCP is the preferred option for treating CBDS and gallstones **(European Association for the Study of the Liver, 2016).** Nevertheless, the efficacy of ERCP is limited in a significant proportion of cases (40%-60%). This is primarily attributed to spontaneous stone passage, unsuccessful CBDS removal, and residual stones **(Sharma et al., 2012; Moller et al., 2014).** Moreover, it carries the risk (5-15%) of significant short- and long-term complications **(Reinders et al., 2011; Omar et al., 2015; Dumonceau et al., 2020; Johnson et al., 2020).**

Recently, certain studies have shown that a substantial proportion of CBDS (10-90%) can pass spontaneously through the sphincter of Oddi into the duodenum **(Lefemine and Morgan, 2011; Sharma et al., 2012; Gao et al., 2013; Moller et al., 2014; Khoury et al., 2019; Ding et al., 2021).** These findings support the conservative treatment for CBDS that has the chance of spontaneous migration, and this may reduce the need for unnecessary ERCP and avoid subsequent ERCP-related complications **(El Nakeeb et al., 2016; Andreozzi et al., 2022).** Several factors have been documented to be associated with the spontaneous passage of CBDS. These factors include a single stone smaller than 6 mm, a non-dilated CBD < 10 mm, an asymptomatic patient, and significant intervals between diagnosis and ERCP **(Gao et al., 2013; Sanguanlosit et al., 2020; Saito et al., 2023).** Conversely, many experts see that relying on spontaneous migration may not be the optimal option for patients with CBDS, especially those who are symptomatic, and these patients have a significant risk of complications if endoscopic or surgical interventions are postponed **(Benjaminov et al., 2013; da Costa et al., 2015).**

To date, the natural history of CBDS is not fully understood because of the lack of long-term studies assessing the outcome of the spontaneous passage of CBDS **(Andreozzi et al., 2022).** Consequently, the optimal management of symptomatic small CBDS is still a subject of debate **(Sharma et al., 2012; Sanguanlosit et al., 2020).**

Frossard et al. (2000) reported a spontaneous migration rate of 22.2 % for CBDS < 8 mm and 4.3% for CBDS ≥ 8 mm. They recommended endoscopic stone extraction before LC for patients with CBDS ≥ 8 mm and a conservative approach for spontaneous stone migration for patients with CBDS < 8 mm. They found a high risk of acute pancreatitis with spontaneous stone migration and advised that surgery should not be delayed too much in such a

case. **Collins et al. (2004)** observed that approximately one-third (12 out of 34) of silent CBDS, which the IOC confirmed during LC, spontaneously passed within six weeks after the operation. This outcome suggests that unnecessary ERCP can be avoided in such cases, and they recommended short-term conservative treatment for asymptomatic CBDS after LC.

Tranter and Thompson (2003) evaluated 1000 patients undergoing LC with or without LCBDE to detect the spontaneous passage rate of CBDS and their relation to patient presentation. They found that 390 of 532 patients (73.3%) had evidence of CBDS before cholecystectomy passed spontaneously. They reported that the spontaneous passage of CBDS was more frequent in patients diagnosed with biliary colic, pancreatitis, and cholecystitis. However, spontaneous passage was found to be less common in patients presenting with jaundice. They explained that jaundice patients may be treated more rapidly than other patients, thereby reducing the time for spontaneous passage. **Lefemine and Morgan (2011)** retrospectively investigated 108 jaundiced patients due to CBDS managed surgically with LC and IOC with or without CBD exploration. They found that CBDS passes spontaneously in 60 patients (55.6%) within approximately four weeks, preventing surgical or endoscopic bile duct intervention for the CBDS. The highest reported rates of spontaneous CBDS passage in these previous two studies were attributed to non-strict included patient criteria with CBDS, such as just a history of jaundice, cholangitis, pancreatitis, elevated bilirubin level, or a dilated CBD **(Gao et al., 2013).**

In a large retrospective cohort analysis, **Moller et al. (2014)** analyzed 3828 patients who underwent conservative treatment and six different interventions to clear the CBDS detected during LC by IOC. They reported unfavorable outcomes of conservative treatment (15.9% vs. 8.9%, 36.9% vs. 12.5%, and 26.5% vs. 18.3%) for < 4 mm, 4-8 mm, and > 8 mm CBDS compared to combined alternative interventions. He concluded that CBDS, even small stones, found during cholecystectomy may not respond well to conservative treatment. A prospective randomized controlled trial by **El Nakeeb et al. (2016)** evaluated 100 patients with CBDS and gallbladder stones treated equally with conservative treatment or endoscopic stone extraction followed by LC and the IOC. They showed a significantly higher success rate in the conservative group (76% vs. 52%, $P < 0.01$). They reported successful endoscopic extraction of CBDS in 26 patients (52%) and spontaneous passage in 19 patients (38%) in the ERCP group, and spontaneous CBDS passage in 38 patients (76%) in the conservative group and 12 patients (24%) failed and required another intervention.

Andreozzi et al. (2022) retrospectively evaluated 1016 patients with CBDS undergoing ERCP within one year. The CBDS was confirmed strictly before the ERCP. They reported no stones at ERCP in 179 patients (17.6%). The spontaneous passage rate was 6.2% (14 patients) when ERCP was performed within 6 hours from diagnosis, 18.5% (114 patients) between 7 hours and 7 days, 24.6% (32 patients) between 8 and 29 days, and 43.2% (19 patients) after 30 days. The spontaneous migration rate was 29.9% for sludge or CBDS ≤ 5 mm in size, 8.7% for CBDS between 6 and 10 mm, and 7.2% for CBDS larger than 10 mm.

Our study revealed a 10.6% and 22.9% spontaneous passage rate in the ERCP and conservative group, respectively. The ERCP group had a significantly higher overall success rate (96.5% vs. 22.9%, $P < 0.001$). This result was comparable with many recent studies. In their research, **Saito et al. (2023)** reported a 6.2%

spontaneous passage rate for CBDS during the interval between diagnosis and ERCP. According to **Sanguanlosit et al. (2020)**, only 19.8% of cholangitis patients passed their stones spontaneously before ERCP, while **Sperna Weiland et al. (2023)** found no CBDS in 155 patients (22%) who underwent ERCP.

The size of the CBDS is a crucial factor that impacts the likelihood of spontaneous passage and the choice of management strategy **(Frossard et al., 2000; Sperna Weiland et al., 2023).** Nevertheless, it may not be advisable to rely solely on spontaneous migration as a treatment strategy for MRCP-proven CBDS **(Benjaminov et al., 2013; da Costa et al., 2015).** We analyzed the relation between the three size categories and the spontaneous passage rate. Our study revealed a significantly higher spontaneous passage rate of class I CBDS (less than 3 mm) in the conservative group (29.6% vs. 78.3%, $P < 0.001$). Also, it revealed a significantly higher spontaneous passage rate of the whole class I CBDS vs. The other two categories (52% vs. 1.7%, $P < 0.0001$). Many studies were like our result regarding the CBDS size liable for spontaneous passage. **Ding et al. (2021)** found that CBDS with a diameter of about 0.33 cm were more likely to pass into the intestines spontaneously. **Khoury et al. (2019)** found that a stone larger than 3.5 mm had a low spontaneous passage rate with 71% sensitivity and 69% specificity. Also, **Sanguanlosit et al. (2020)** revealed that CBDS size < 5 mm tends to pass spontaneously in cholangitis patients. And with ROC curve analysis, they found that CBDS under 3.85 mm were more likely to pass spontaneously with good sensitivity (81.8%) and specificity (78.9%).

Our study revealed a significantly reduced useless procedure rate in the ERCP group (14.1% vs. 77.1%, $P < 0.001$). On the contrary, a retrospective multicenter study by **Andreozzi et al. (2022)** analyzed 1016 patients with CBDS undergoing ERCP reported a useless ERCP in 179 patients (17.6%), in 14 patients (6.2%) when ERCP was performed within 6 hours from diagnosis, in 114 patients (18.5%) between 7 hours and 7 days, in 32 patients (24.6%) between 8 and 29 days, and 19 patients (43.2%) after 30 days. They recommended delaying ERCP for seven days for patients with sludge or CBDS ≤ 5 mm to avoid unnecessary ERCP. Also, **El Nakeeb et al. (2016)** reported a significantly high useless procedure rate in the ERCP group (48% vs. 24%, $P < 0.01$).

The risk of adverse events associated with persistent stones during the observation period and interventional complications are essential factors to be considered when deciding between conservative and interventional management **(Andreozzi et al., 2022).** Our study revealed no significant morbidity difference between groups (2.4% vs. 7.2%, $P = 0.14$). **El Nakeeb et al. (2016)** reported significantly higher post-ERCP pancreatitis in the ERCP group (16% vs. 4%, $P = 0.04$). **Andreozzi et al. (2022)** reported a complication rate of 12% in the ERCP group and no adverse events involving patients awaiting ERCP. This difference may be attributed to the long mean interval between diagnosis and ERCP (6.0 ±13.2 days). **Frossard et al. (2000)** reported adverse events in 2 patients (17%) in the conservative treatment group. But the retrospective design of these studies makes it unsuitable to evaluate this issue. **Sperna Weiland et al. (2023)** reported 2/29 patients with CBDS experienced cholangitis between diagnosis and ERCP (32 and 93 days). **Collins et al. (2004)** reported no complications during the conservative time. **Saito et al. (2023)** reported that the overall ERCP-related complications were 8.4% (4.1% for pancreatitis, 2.1% for bleeding, 1.7% for cholangitis, and 0.8% for perforation). The rate of

ERCP-related complications did not differ significantly between patients with and without spontaneously passed CBDS (7.7% vs. 8.5%, P = 0.96). Most research **(Khashab et al., 2012; Tan et al., 2018)** recommends ERCP be performed on cholangitis patients as soon as possible, preferably within 24 hours, as the risk of morbidity and mortality increases when ERCP is delayed.

Hospital stays and total costs are among the main factors on which health strategies are based, especially in poor countries. The longer the hospital stays, the greater the health costs generated. Our study revealed significantly shorter hospital stays (5 vs. 8 days, $P < 0.001$) and reduced costs (1810 vs. 2250 US$, $P < 0.001$) in the ERCP group. In contrast, **El Nakeeb et al. (2016)** observed a statistically significant increase in net cost within the ERCP group (1810 vs. 2250 US$, $P < 0.001$). Also, **Andreozzi et al. (2022)** reported that the conservative method might provide a more cost-effective and safer alternative than the ERCP approach for patients with CBDS ≤ 5 mm. Our reduced cost may be attributed to the short interval between the diagnosis and the ERCP and the LC in contrast to the conservative group in which LC was performed at least after five days of hospitalization and medical treatment.

Our study revealed no significant difference between groups in recurrent biliary symptoms (2.4% vs. 7.2%, P = 0.14). On the contrary, **El Nakeeb et al. (2016)** reported significantly recurrent biliary symptoms after one year in the ERCP group (10% vs. 0%, P = 0.02)

The time limit during which it is safe to wait for the spontaneous passage of CBDS is crucial, as theoretically and practically, a delay between a patient's diagnosis and the ERCP procedure could enhance the likelihood of CBDS passing spontaneously but, at the same time, carries a high risk of developing stone-related complications (**Al-Jiffry et al., 2016; Andreozzi et al., 2022).** In their study, **Sperna Weiland et al. (2023)** observed that a time interval beyond two days between the performance of diagnostic imaging and ERCP decreases the possibility of a positive ERCP. According to **Saito et al. (2023),** the cumulative diagnostic rate of spontaneous CBDS migration was 6.2% during an average period of 5 days. In a study conducted by **Frossrad et al. (2000),** the rates of spontaneous migration of CBDS were observed over different time intervals between diagnosis and ERCP. The study reported migration rates of 0%, 21%, and 20% within 6 hours, 6 to 3 days, and 3 to 27 days, respectively. Similarly, **Andreozzi et al. (2022)** investigated the spontaneous migration of CBDS in relation to the timing of ERCP. The study found migration rates of 6.2%, 18.5%, 24.6%, and 43.2% when ERCP was performed within 6 hours, 7 hours to 7 days, 8 to 29 days, and after 30 days of the imaging investigation, respectively. **Collins et al. (2004)** found that 35% of silent CBDS detected by IOC during LC could pass spontaneously within six weeks after the operation.

The asymptomatic patient was a documented factor for the spontaneous passage of CBDS **(Gao et al., 2013; Sanguanlosit et al., 2020; Saito et al., 2023). Saito et al. (2023)** attributed the higher probability of spontaneous CBDS migration in patients with asymptomatic CBDS mainly to the longer intervals between imaging diagnosis and surgical intervention. They recommended early ERCP for symptomatic CBDS and elective ERCP for those with asymptomatic CBDS. Also, **Tan et al. (2018)** reported that using a "wait and observe" approach, without immediate intervention, for patients with small CBDS identified during IOC in LC seems to be a safe strategy. According to **Tranter and Thompson (2003),** the spontaneous passage of CBDS was more frequent in patients diagnosed with biliary colic, pancreatitis, and cholecystitis. However,

spontaneous passage was found to be less common in patients presenting with jaundice. They explained that jaundice patients may be treated more rapidly than other patients, thereby reducing the time for spontaneous passage.

Strengths and limitations

Our study has several strengths as it is a randomized controlled trial with a homogeneity of imaging studies to diagnose CBDS. Also, it is one of the first studies comparing ERCP and conservative treatment for symptomatic CBDS. A few limitations should be addressed. Firstly, we did not conduct additional testing, such as intraductal ultrasound, to evaluate residual CBDS following cholangiography and stone removal, and secondly, the study was single-blinded.

Conclusion

Symptomatic CBDS, even small-sized, should be managed surgically as early as possible. Endoscopic stone extraction has a high success rate and a lower hospital stay and total cost. The conservative treatment for symptomatic small CBDS is useless and should not be practiced.

List of Abbreviation

- ASA American Society of Anesthesiologists
- BMI Body Mass Index
- CBD Common Bile Duct
- CBDS Common Bile Duct Stones
- CT Computed Tomography
- ERC Endoscopic Retrograde Cholangiography
- ERCP Endoscopic Retrograde CholangioPancreatography
- IOC Intraoperative Cholangiogram
- IQR InterQuartile Range
- LC Laparoscopic Cholecystectomy
- LCBDE Laparoscopic Common Bile Duct Exploration
- LC-ERCP Laparoscopic Cholecystectomy-Endoscopic Retrograde CholangioPancreatography
- MRCP Magnetic Resonance CholangioPancreatography
- SAGES Society of American Gastrointestinal and Endoscopic Surgeons
- SD Standard Deviation

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