Saline irrigation for reducing the recurrence of common bile duct stones after lithotripsy: a randomized controlled trial

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Summary

Background Mechanical lithotripsy produces stone fragments that are not easily detected by cholangiography and is a potential cause of recurrence of common bile duct stones (CBDS). This study aims to clarify whether 100 ml saline irrigation after mechanical lithotripsy reduces the recurrent rate of CBDS.

Methods In this randomized controlled trial performed at the Surgical Endoscopy Center, the First Hospital of Lanzhou University between May 10, 2019, and Dec 31, 2020, patients undergoing endoscopic mechanical lithotripsy were randomly assigned to receive saline irrigation (study group) or no irrigation (control group). The saline irrigation was given 100 ml saline pulse irrigation after cholangiography showed no residual stones. Patients were followed up for at least 24 months after endoscopic stone removal to assess the recurrence of CBDS. This study was registered with ClinicalTrials.gov (NCT03937037).

Findings During the median follow-up period of 35.6 months (interquartile range, 26.0–40.7), 43 of the 180 patients had stone recurrence (24%). The frequency of recurrence of CBD stones was 12.22% in the saline irrigation group and 35.56% in the control group, with a difference of 23.33% between the two groups (95% confidence interval [CI], 11.35%–35.32%, $p < 0.001$). Multivariable Cox proportional hazards analyses showed that constipation (hazard risk [HR] 2.42; 95% CI, 1.22–4.80, $p = 0.012$), periampullary diverticulum (PAD) (HR 3.06; 95% CI, 1.62–5.79, $p < 0.001$), and total to direct bilirubin ratio (HR 1.48; 95% CI, 1.21–1.81, $p < 0.001$) were independent risk factors for the recurrence of CBDS. Saline irrigation was the only preventive factor for the recurrence of CBDS (HR 0.22; 95% CI, 0.11–0.44, $p < 0.001$).

Interpretation For patients with CBDS requiring mechanical lithotripsy, 100 ml saline irrigation effectively reduces the recurrent rate of CBDS after endoscopic stone removal.

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Keywords: Saline irrigation; Endoscopic retrograde cholangiopancreatography; Common bile duct stones; Lithotripsy; Recurrence

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Research in context

Evidence before this study

Mechanical lithotripsy is a common technique for the endoscopic management of complex stones. It may produce stone fragments not easily detected by cholangiography and is a potential cause of the recurrence of common bile duct stones (CBDS). Whether saline irrigation can reduce the recurrence of stones after endoscopic stone removal has not been confirmed. We searched PubMed and the Cochrane Library for articles published without language restrictions up to Dec 31, 2022, using combinations of search terms such as "saline irrigation", "common bile duct stones", "recurrence", "stone fragments", and "ERCP". Our search results displayed limited prospective evidence for the association between saline irrigation and the recurrence of common bile duct stones. Only one retrospective study has shown that saline irrigation can reduce stone recurrence, and the small sample size may potentially limit this retrospective study.

Added value of this study

Our study is the first prospective randomized controlled study of the association between saline irrigation and stone recurrence after mechanical lithotripsy. Our research results show that 100 ml saline irrigation after mechanical lithotripsy reduces the stone recurrence rate. Constipation and periampullary diverticulum (PAD) are independent risk factors for the recurrence of CBDS. In contrast, saline irrigation is a preventive factor for the recurrence of CBDS.

Implications of all the available evidence

The residual stone fragment is a risk factor for the recurrence of CBDS. Still, saline irrigation after endoscopic stone removal is not routine, which increases the probability of choledocholithiasis recurrence. Our study adds significant prospective evidence that saline irrigation reduces the recurrence rate of CBDS. Saline irrigation after endoscopic stone removal is beneficial to prevent stone recurrence and reduce the reoperation rate of patients with CBDS.

Introduction

Common bile duct stones (CBDS) are the most common digestive diseases, and endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (EST) and/or endoscopic papillary balloon dilation (EPBD) is currently the first-line treatment for CBDS due to its effectiveness and minimal invasiveness.[1–3] However, the recurrence of CBDS after endoscopic stones extraction has been a troubling clinical problem. It has been reported that the recurrence rate of CBDS is between 4% and 24% after ERCP.[4,5]

Mechanical lithotripsy is a common technical procedure that makes giant stones easy to remove.[6] However, mechanical lithotripsy is one of the important risk factors for CBD stone recurrence.[7] Small stone fragments or bile sludge left after lithotripsy may become the primary nidus of stone recurrence.[8] A retrospective study found that the residual stone rate after endoscopic extraction was 25.9% (14/54).[9] Another trial reported a residual stone rate of 50% (15/30) in patients with multiple stones after endoscopic stone removal.[10] Our previous prospective self-controlled study of 47 patients who underwent lithotripsy and stone removal by ERCP found that although there were no stone residues on cholangiography, SpyGlass DS found that there were no stone fragments or biliary sludge residues in only 15% of the cases.[11] Taken together, the literature and our previous study show that cholangiography after endoscopic extraction does not detect residual stone fragments and biliary sludge. These tiny missed stone fragments become one of the reasons for stone recurrence. Some studies have reported that saline irrigation can reduce the residual stone rate after endoscopic stone removal, especially if the lithotripsy technique is required.[7,9,10,12] Our previous study confirmed that 94% of patients were free of stone fragments and biliary sludge after intermittent irrigation with 100 ml saline.[11] However, there are few reports about residual stone fragments and the recurrence of CBDS. Whether saline irrigation can reduce the recurrence of stones after endoscopic stone removal has not been confirmed by prospective randomized controlled trials.

We designed a randomized controlled trial to compare the stone recurrence rate in the saline irrigation group after mechanical lithotripsy with that in the control group.

Methods

Study design and participants

This double-blinded, single-center, randomized controlled trial was performed in the Surgical Endoscopy Center, the First Hospital of Lanzhou University. Patients aged ≥18 years with CBDS (stone size ≥1.2 cm, ≤3 cm) who planned to undergo ERCP. The exclusion criteria included contraindications for ERCP, a history of previous EST or EPBD, coagulation dysfunction (international normalized ratio >1.5), and thrombocytopenia (platelet count <50 × 10^9 cells per L) or current administration of antiplatelet or anticoagulation drugs, previous RouxenY or Bismuth II gastrectomy, malignant disease, common bile duct stricture, and preexisting conditions such as cholangitis with septic shock, suppurative cholangitis with non-septic, severe liver disease, acute pancreatitis, primary sclerosing cholangitis, known Mirizzi syndrome, intrahepatic bile duct stones, biliary-duodenal fistula, or gastrointestinal bleeding, patients with stones detected within 6 months after the first endoscopic procedure. Pregnant women were also excluded. Preoperatively, indications or contraindications for ERCP were evaluated by endoscopists and anesthesiologists. The ethics committee of the First Hospital of Lanzhou University approved the study protocol. All patients or their legal representatives provided written informed consent. The study was performed according to the Helsinki Declaration and Clinical Practice Guidelines.

Randomization and masking

The patients were randomly divided into two groups (1:1). After occlusion cholangiography was used to confirm that there were no residual stones, the irrigation group received pulse irrigation with 100 ml saline, and the operation was completed in the control group. Randomization was completed by an independent statistician using a computer-generated random number with a block size of ten. The randomization allocation was done after the endoscopist had removed the stone. Specifically, an independent researcher would inform the endoscopist of the patient's assigned group after the stone removal and then require the endoscopist to complete the saline irrigation or end the operation. The patients and outcome assessors were blinded to the intervention allocation.

Procedures

Patients received local pharyngeal anesthesia and non-intubation sedation anesthesia during ERCP. All patients were not routinely given prophylactic antibiotics. All endoscopists had performed at least 1000 ERCP cases. All patients underwent continuous cardiopulmonary monitoring during anesthesia and the operation. The procedure for endoscopic stone extraction was identical to that described in a previous clinical study conducted at our center.[11] In brief, all patients underwent sphincterotomy using the endo-cut mode after successful cannulation, followed by sphincteroplasty using a controlled radial expansion balloon (Boston Scientific, Cork, Ireland) of appropriate size, which was no more than the diameter of the stones and the distal common bile duct. Subsequent mechanical lithotripsy (Boston Scientific, Marlborough, MA, United States) was performed using a lithotripter-compatible basket to facilitate stone extraction using a basket or stone removal balloon. The endoscopists and radiologists evaluated the occlusive cholangiography, and the bile duct was considered clean if there was a consensus that there were no remaining stones. After the absence of residual stones was confirmed, patients in the irrigation group received pulsed irrigation with 100 ml of saline through a catheter. Most adverse events related to ERCP were detected within 24 h of the procedure. We routinely assessed the adverse events, including post-ERCP pancreatitis, acute cholangitis, cholecystitis, perforation, and bleeding at 24 and 48 h after the procedure, by recording symptoms and signs and performing laboratory tests and imaging examinations if necessary.

Follow-up

All enrolled patients received liver function and abdominal imaging every 6 months after the initial endoscopic stone removal. The procedure was liver function and abdominal ultrasound or abdominal computed tomography (CT) screening first, and further magnetic resonance cholangiopancreatography (MRCP) was required if there were abnormal liver enzymes or bile enzymes or if CBDS or abnormal density in the common bile duct or common bile duct dilatation >8 mm (with gallbladder in situ) or >10 mm (with the gallbladder has removed) was found. All patients were followed up for at least 24 months after the initial endoscopic stone removal. Patients presented to the emergency department or outpatient clinic if they had symptoms of fever, chills, abdominal pain, or jaundice during the follow-up period. MRCP was performed according to the clinical manifestations, blood routine and liver function tests, and ultrasonography if the recurrence of bile duct stones was highly likely. When CBDS were diagnosed, endoscopic removal of the stones was performed again.

Outcomes

The primary endpoint was stone recurrence. Common bile duct stone recurrence was defined as the rediscovery of CBDS more than 6 months after the previous procedure.[13]

The secondary outcomes included post-ERCP complications and operation time. The post-ERCP complications included cholangitis, post-ERCP pancreatitis, gastrointestinal bleeding, acute cholecystitis, and perforation. Cholangitis was defined as fever (body temperature >38 °C) for 24–48 h after ERCP, often with chills, considered to be of biliary origin, but without evidence of other concomitant infections.[14] Post-ERCP pancreatitis referred to new or aggravated of abdominal pain after ERCP, accompanied by serum amylase or lipase levels that were more than 3 times higher than normal at 24 h after ERCP.[15] Acute cholecystitis was defined as signs of inflammation in the right upper quadrant, systemic inflammatory signs, and imaging features of acute cholecystitis without any clinical or imaging indications before ERCP.[16] Gastrointestinal bleeding was defined as hematemesis and/or hematochezia or a decrease in hemoglobin of more than 2 g/dL after ERCP.[15] Perforation was defined as the presence of gas or contrast extravasation outside the gastrointestinal tract confirmed by imaging.[15]

Additional monitored parameters included the classification of the periampullary diverticulum, the diameter of CBD, the maximum size of CBDS, the number of stones, constipation, and any other adverse events requiring a prolonged hospital stay. Constipation was defined as decreased frequency of defecation (less than 3 times per week), dry stools, and/or difficult defecation.[17] Constipation is diagnosed according to Rome IV criteria.[18]

Statistical analysis

Based on previous research[19] and our previous pilot data, we assumed a stone recurrence rate of 30% in the control group (without irrigation) and 12% in the irrigation group. Under the power of 80% and the level of 0.05, 80 patients were needed in each group, and the loss to follow-up rate was expected to be 10%. Finally, 88 patients were needed in each group, and a total of 176 patients were enrolled. Primary and secondary outcome analyses were based on the per-protocol population, which included all patients who had finished at least 24 months of follow-up. Other analyses were based on intention-to-treat analysis (all randomly assigned patients finished ERCP). For the primary outcome (recurrence), the difference in the ratio between the two groups and the 95% confidence interval (CI) were calculated. Basic characteristics and clinical information were presented as the means and standard deviations for normal quantitative variables (assessed by histogram), and for skewed continuous variables, medians and inter quartile ranges (IQR) were used, and counts and percentages were used for dichotomous variables. Tests between two groups were conducted using the t test, Wilcoxon test, chi-square test, and Fisher's exact test, as appropriate. The 2-year rate of recurrence in the two groups was described by Kaplan–Meier curves and compared with a log-rank test. Factors associated with recurrence were analyzed using a Cox proportional hazards model, with group and the other basic and clinical factors treated as covariates. Variables with a value of $p < 0.10$ in univariate analysis were considered for adjustments in the multivariable model. No interim analysis was performed. All tests were two-sided, and a p value of <0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., NC, United States).

Ethics statement

This study has been approved by the Ethics Committee of The First Hospital of Lanzhou University (No.LDYYMENG2019-0027) and conducted by the ethical principles of the Declaration of Helsinki. Participants gave informed consent to participate in the study before the procedure.

Role of the funding source

The funder of the study had no role in study design, patient recruitment, data collection and analysis, interpretation of the data, or writing of the report. The corresponding author (YP, YJQ and WBM) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Baseline patient characteristics

Between May 10, 2019, and Dec 31, 2020, 308 consecutive patients with CBDS scheduled for ERCP requiring lithotripsy were assessed for eligibility. After screening, 119 patients were excluded (45 patients did not meet the inclusion criteria and 74 patients met the exclusion criteria; Fig. 1). The remaining 189 patients were randomly assigned to the saline irrigation group and control group. Seven patients were lost to follow-up, and 2 patients had stones detected within 6 months after the first endoscopic procedure. Finally, a total of 180 patients were included in the per-protocol population (saline irrigation group [n = 90], control group [n = 90]), all of whom completed at least 24 months of follow-up. (Fig. 1). The baseline characteristics of the enrolled patients are shown in Table 1. There was no significant difference in the baseline characteristics between the two groups.

Primary outcome

During the median follow-up period of 35.6 months (IQR, 26.0–40.7), 43 of the 180 patients had stone recurrence (24%). Median follow-up months and IQRs for saline irrigation and control groups were 36.9 (32.4–41.9) and 32.1 (13.3–39.2), respectively. The recurrence of CBDS was detected in 11 of 90 patients (12.22%) and 32 of 90 patients (35.56%) in the saline irrigation group and the control group, respectively, with a difference of 23.33% between the two groups (95% CI, 11.35%–35.32%, $p < 0.001$). The Kaplan–Meier plot also showed that the recurrence of CBDS in the saline irrigation group was significantly lower than that in the control group (log-rank $p < 0.001$) (Fig. 2).

Secondary outcome

Following ERCP, procedure-related complications occurred in 19 of 180 patients (10.6%); 13 (7%) of 180 patients had acute cholangitis, 4 (2%) patients had post-ERCP pancreatitis, and 2 (1%) patients had acute cholecystitis. There was no gastrointestinal bleeding or perforation (Table 2). However, all procedure-induced complications resolved spontaneously and uneventfully with conservative management. No clinically significant adverse events were reported, and no deaths occurred in association with the complications. The median duration of the procedure was 47.8 ± 7.5 min in the saline irrigation group and 43.5 ± 7.6 min in the control group. Compared with the control group, the procedure time was approximately 4 min longer in the saline irrigation group ($p < 0.001$) (Table 3).

Risk factor analysis

Univariate analyses showed that constipation, periampullary diverticulum (PAD), and the total to direct

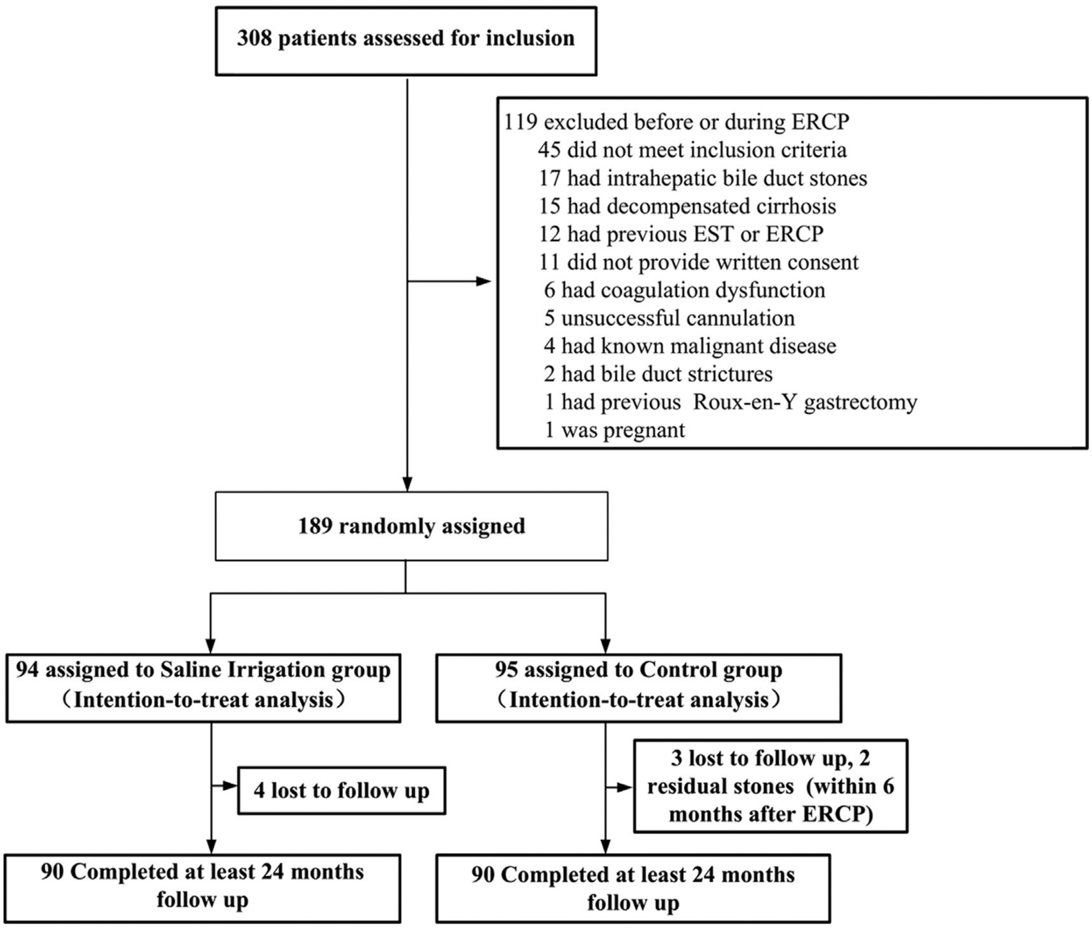

Fig. 1: Flow chart. ERCP = endoscopic retrograde cholangiopancreatography. EST = endoscopic sphincterotomy.

bilirubin ratio were associated with significantly increased recurrence of CBDS. Saline irrigation was a preventive factor for the recurrence of CBDS. Multivariate analyses showed that constipation (hazard risk [HR] 2.42; 95% CI, 1.22–4.80, p = 0.012), PAD (HR 3.06; 95% CI, 1.62–5.79, p < 0.001), and the total to direct bilirubin ratio (HR 1.48; 95% CI, 1.21–1.81, p < 0.001) were independent risk factors for recurrence of CBD. Saline irrigation was the only preventive factor for the recurrence of CBD stones (HR 0.22; 95% CI, 0.11–0.44, p < 0.001) (Table 4).

The stone recurrence rate was significantly higher in patients with PAD than in those without PAD (p = 0.0001, Supplementary Fig. S1A). Saline irrigation can reduce the recurrence rate of stones in patients with PAD (p < 0.0001, Fig. 3A). Due to the small number of Li Tanaka subtypes,[20] to facilitate further analysis, according to the relationship between the diverticulum and the papilla, the different types of diverticulum were combined into the internal papilla of the diverticulum (types I and IIa) and the external papilla of the diverticulum (types IIb, III, IV). The recurrence rate of CBDS was significantly higher in patients with intra diverticulum papillae than in those with extra diverticular papilla (p < 0.001, Supplementary Fig.S1B). Saline irrigation reduced the recurrence rate of stones in patients with intra diverticulum papillae (p = 0.0005, Fig. 3B). Compared with patients without constipation, patients with constipation had an increased recurrence rate of stones (p = 0.0001, Supplementary Fig.S1C). Saline irrigation also reduced stone recurrence in patients with constipation (p = 0.023, Fig. 3C). In patients with constipation and PAD (especially intra diverticulum papillae), the recurrence rate of stones in the irrigation group was lower than that in the control group, and the difference between the two groups was statistically significant (p = 0.016, Fig. 3D).

Discussion

Stone fragments and bile sludge produced by lithotripsy are easily missed by cholangiography. Whether stone fragments left in the bile duct are the source of stone recurrence and whether removing these stone

Variables	Total (N = 189)	Salt (N = 94)	Control (N = 95)	p value
Male, N (%)	103 (54.5)	52 (55.3)	51 (53.7)	0.82
Age (years, mean ± SD)	63.7 ± 14.3	63.6 ± 14.8	63.8 ± 13.9	0.95
BMI (kg/m^2, mean ± SD)	23.1 ± 3.6	22.7 ± 3.8	23.6 ± 3.4	0.09
Comorbidities, N (%)				
Diabetes	35 (18.5)	18 (19.2)	17 (17.9)	0.82
Hypertension	72 (38.1)	40 (42.6)	32 (33.7)	0.21
CVD	6 (3.2)	3 (3.2)	3 (3.2)	1.00
COPD	3 (1.6)	2 (2.1)	1 (1.1)	0.62
Constipation, N (%)	24 (12.7)	10 (10.6)	14 (14.7)	0.40
Defecation frequency, N (%)				0.23
<3 times/week	28 (14.8)	11 (11.7)	17 (17.9)	
≥3 times/week	161 (85.2)	83 (88.3)	78 (82.1)	
Dry stool, N (%)	24 (12.7)	11 (11.7)	13 (13.7)	0.68
Difficult defecation, N (%)	30 (15.9)	12 (12.8)	18 (19.0)	0.24
History of cholecystectomy, N (%)	95 (50.3)	46 (48.9)	49 (51.6)	0.72
Gallbladder stones, N (%)	56 (29.6)	31 (33.0)	25 (26.3)	0.32
TBIL (μmol/L, median (IQR))	36.9 (18.9, 91.3)	33.5 (18.2, 71.8)	39.6 (19.8, 100.0)	0.51
TBIL/DBIL	3.0 ± 1.4	3.1 ± 1.5	2.9 ± 1.4	0.23

NOTE. SD, Standard deviation, IQR, Inter quartile ranges, BMI, Body mass index, CVD, Cardiovascular disease, COPD, Chronic obstructive pulmonary disease, TBIL, Total bilirubin, DBIL, Direct bilirubin.

Table 1: **Basic and clinical characteristics of the patients.**

fragments can prevent stone recurrence is not completely clear. In this study, our results confirm that after mechanical lithotripsy, pulsed irrigation with 100 ml saline reduces stone recurrence.

Mechanical lithotripsy is an effective and safe technique for endoscopic stone removal.[6] However, a large number of stone fragments and bile sludge are produced after lithotripsy. Due to the low sensitivity of cholangiography, it is easy to miss the diagnosis, especially when the stone fragments are smaller than 4 mm or the bile duct is dilated.[10,21] Ang TL et al. reported that 40% (28/70) of patients with no filling defect detected by cholangiography had residual stones by IDUS.[12] Lee et al. used direct peroral cholangioscopy (DPOC) and balloon cholangiography to evaluate residual bile duct stones and found that 28.3% (13/46) of the patients had residual bile duct stones, which were missed by balloon cholangiography.[21] In our previous study, 47 patients with no stones detected by cholangiography after endoscopic lithotripsy and stone removal, the Spy Glass DS showed that 40/47 (85%) of the cases had stone fragments and sludge residue in the biliary tract.[11]

In response to the problem of residual stones after ERCP, Ang TL et al. reported that an average of 48 ml of normal saline could flush out most of the residual stones.[12] Ahn DW et al. reported that the residual stone rate in the irrigation group was lower than that in the nonirrigation group (6.8% vs. 22.7%, p = 0.010), and the difference between the two groups was more significant in patients with multiple stones (12.1% vs. 50.0%,

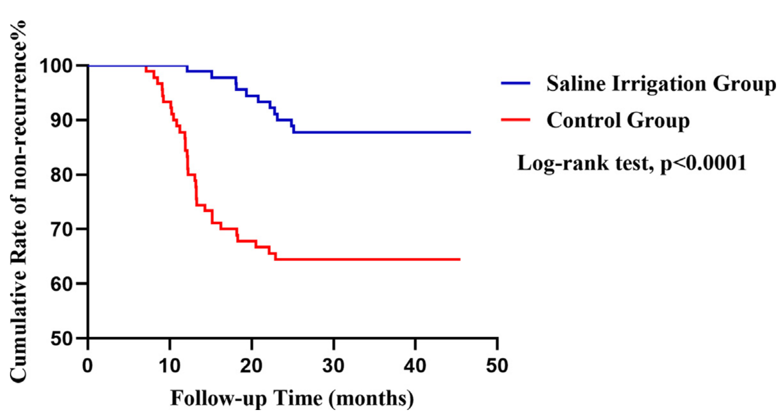

Fig. 2: Kaplan–Meier curves showing the rate of common bile duct stone recurrence.

Variables	Total	Salt (N = 90)	Control (N = 90)	p value
Recurrence, N (%)	43 (23.9)	11 (12.2)	32 (35.6)	<0.001
Pancreatitis, N (%)	4 (2.2)	1 (1.1)	3 (3.3)	0.62
Cholangitis, N (%)	13 (7.2)	8 (8.9)	5 (5.6)	0.39
Cholecystitis, N (%)	2 (1.1)	0	2 (2.2)	0.50
Bleeding, N (%)	0	0	0	
Perforation, N (%)	0	0	0	
Procedure time (min, mean ± SD)	45.6 ± 7.8	47.8 ± 7.5	43.5 ± 7.6	<0.001

NOTE. SD, Standard deviation.

Table 2: **Primary and secondary outcome.**

$p < 0.05$).[10] Our previous study showed that the residual stone rate of patients with mechanical lithotripsy was as low as 6% after endoscopic stone removal with 100 ml saline pulse irrigation,[11] which was consistent with the study of Endo R.[7] In conclusion, saline irrigation can reduce the residual stone rate after endoscopic stone extraction. Several studies have suggested that mechanical lithotripsy is associated with the recurrence of CBDS, which may be due to the residual stone fragments generated by lithotripsy as the basis for subsequent stone recurrence.[9,10,12]

However, few studies have reported on residual stone fragments and stone recurrence. Only one retrospective study showed that saline irrigation after ERCP could significantly reduce the stone recurrence rate, with recurrence rates reported as 13.9% (5/36) in the irrigation group and 44.6% (25/56) in the control group ($p = 0.001$).[7] In our clinical study, the recurrence rate of CBDS was 12.22% (11/90) in the irrigation group and 35.56% (32/90) in the control group, which was slightly lower than that in the above studies, probably due to the differences in sample size, patient population characteristics, and the definition of stone recurrence. The present study differs from previous studies in that we conducted a prospective, randomized, controlled study in which all patients included required mechanical lithotripsy.

Variables	Total (N = 189)	Salt (N = 94)	Control (N = 95)	p value
Common bile duct diameter (mm, mean ± SD)	16.6 ± 4.2	16.6 ± 4.0	16.6 ± 4.5	0.99
Maximum size of stones (mm, mean ± SD)	15.0 ± 4.3	15.0 ± 4.1	15.0 ± 4.5	0.99
Number of stones, N (%)				0.70
1	46 (24.3)	24 (25.5)	22 (23.2)	
≥2	143 (75.7)	70 (74.5)	73 (76.8)	
EST, N (%)	189 (100.0)	94 (100.0)	95 (100.0)	
EST long (mm, mean ± SD)	4.4 ± 1.4	4.4 ± 1.4	4.4 ± 1.4	0.98
EPBD, N (%)	189 (100.0)	94 (100.0)	95 (100.0)	
Dilation diameter (mm, mean ± SD)	10.2 ± 1.5	10.1 ± 1.6	10.4 ± 1.4	0.18
Dilation duration 30s, N (%)	189 (100.0)	94 (100.0)	95 (100.0)	
PAD, N (%)	58 (30.7)	30 (31.9)	28 (29.5)	0.72
Intra diverticular papilla (I, IIa)	31 (53.4)	12 (40.0)	19 (67.9)	0.03
Extra diverticular papilla (IIb, III, IV)	27 (46.6)	18 (60.0)	9 (32.1)	
Mechanical lithotripsy, N (%)	189 (100.0)	94 (100.0)	95 (100.0)	
Cholangiography confirmed the absence of stones, N (%)	189 (100.0)	94 (100.0)	95 (100.0)	
Fever[a], N (%)	13 (6.9)	8 (8.5)	5 (5.3)	0.38
Abdominal pain[b], N (%)	6 (3.2)	1 (1.1)	5 (5.3)	0.21
White blood cell count ($\geq 10 \times 10^9$/L), N (%)	23 (12.2)	13 (13.8)	10 (10.5)	0.49
Hyperamylasaemia	50 (26.5)	20 (21.3)	30 (31.6)	0.11
Post-ERCP hospital stay	5.0 ± 1.4	5.0 ± 1.3	5.1 ± 1.4	0.88
Hospital costs	32,140 ± 11,793	32,246 ± 13,425	32,036 ± 9990.9	0.90
Follow-up (months, median (IQR))	35.6 (26.0, 40.7)	36.9 (32.4, 41.9)	32.1 (13.3, 39.2)	<0.001

NOTE. SD, Standard deviation, IQR, Inter quartile ranges, EPBD, Endoscopic papillary balloon dilation, EST, Endoscopic sphincterotomy, EPBD, Endoscopic papillary balloon dilatation, PAD, Periampullary diverticulum, ERCP, Endoscopic retrograde cholangiopancreatography. [a]Body temperature higher than 38.5 °C. [b]Numeric rating scale score of 7–10.

Table 3: **Clinical and procedural information.**

Variables	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age	1.00	0.98–1.02	0.79			
Sex (male vs. female)	1.01	0.55–1.84	0.98			
BMI	1.00	0.93–1.08	0.97			
Constipation (yes vs. no)	3.34	1.74–6.41	<0.001	2.82	1.41–5.64	0.003
History of cholecystectomy (yes vs. no)	1.32	0.72–2.40	0.37			
Gallbladder stones (yes vs. no)	0.61	0.29–1.28	0.19			
TBIL/DBIL	1.29	1.07–1.55	0.009	1.52	1.24–1.86	<0.001
PAD(yes vs. no)	3.09	1.69–5.65	<0.001	3.34	1.77–6.31	<0.001
Common bile duct diameter	1.03	0.96–1.10	0.39			
Maximum size of stones	1.00	0.94–1.08	0.93			
Number of stones (>=2 vs. 1)	2.52	0.99–6.41	0.052	2.39	0.93–6.10	0.07
Saline irrigation (yes vs. no)	0.28	0.14–0.55	<0.001	0.20	0.10–0.40	<0.001

NOTE. BMI, Body mass index, TBIL, Total bilirubin, DBIL, Direct bilirubin, PAD, Periampullary diverticulum, HR, Hazard risk, CI, Confidence interval.

Table 4: **Cox proportional hazard model for CBDs recurrence.**

In this study, all patients had common bile duct dilatation, and the common bile duct diameter was 16.6 ± 4.2 mm. Common causes of common bile duct dilatation include bile duct stones, tumor at the lower end of the common bile duct or pancreatic head tumor, congenital biliary dilatation, compensatory dilatation after cholecystectomy, etc.[22,23] Malignant diseases and common bile duct stricture were excluded from this study. MRCP and ERCP were used for the differential diagnosis of congenital bile duct dilatation.[24] There were no patients with congenital bile duct dilatation included in the study. After cholecystectomy, the common bile duct will appear to have the mild compensatory expansion, and the diameter of the common bile duct is generally not more than 10 mm.[25] 95 of the patients included in this study had a history of cholecystectomy, and all of these patients had a common bile duct diameter greater than 10 mm. The cause of common bile duct dilatation in this study may be related to the diameter and number of CBDS in the enrolled patients. The diameter of CBDS in the enrolled patients was between 12 mm and 30 mm, and 75.66% (143/189) of them had multiple stones, which caused biliary obstruction followed by dilatation of the common bile duct.

In our study, PAD was significantly associated with choledocholithiasis recurrence. PAD was a risk factor for choledocholithiasis recurrence, which is consistent with previous studies.[26–28] The recurrence rate of CBDS in patients with PAD was 14%, and the recurrence rate of CBDS in patients with duodenal papilla located in the diverticulum was up to 44%, which was 14 times higher than that of patients with other types of the diverticulum. The larger the diverticulum was, the higher the recurrence rate of CBDS.[29] In this study, the recurrence rate of stones in patients with papillae located in the diverticulum was significantly higher than that in patients with papillae located outside the diverticulum, suggesting that PAD may cause stone recurrence by affecting the function of the duodenal papilla. PAD affects the normal anatomy of the papilla, the lower end of the bile duct and the confluence of the pancreatic duct and bile duct. The closer the PAD is to the papilla, the greater the impact on biliary emptying.[27] If the papilla is located within or very close to the PAD, the appearance, shape, and size of the papilla tend to be altered, which may affect bile excretion. A large PAD may directly compress the common bile duct, resulting in poor biliary excretion and cholestasis.[27]

For patients with internal papilla of the diverticulum, if there are residual stone fragments in the common bile duct, the existence of the diverticulum affects the function of the duodenal papilla and makes the fragments difficult to expel, which may increase the risk of stone recurrence. Risk factor analysis suggests that saline irrigation has the effect of preventing stone recurrence in patients with a diverticular internal papilla, so routine saline irrigation after ERCP is recommended for patients with a diverticular internal papilla.

Based on our study, we believe saline irrigation reduced the recurrence rate of CBDS mainly by reducing the residual small bile duct stones or stone fragments and improving the cleanliness of the bile duct. Several studies have reported that saline irrigation can reduce small residual stones after endoscopic stone extraction.[7,9–11] A variety of factors cause the recurrence of CBDS. Saline irrigation is a safe and effective preventive measure, but it can not completely prevent the recurrence of CBDS. Enterobiliary reflux is a risk factor for choledocholithiasis recurrence.[30] We hypothesized that saline irrigation might be more effective in patients with normal papilla function than in patients with papilla insufficiency. EST resulted in partial loss of duodenal papilla function, and constipation caused

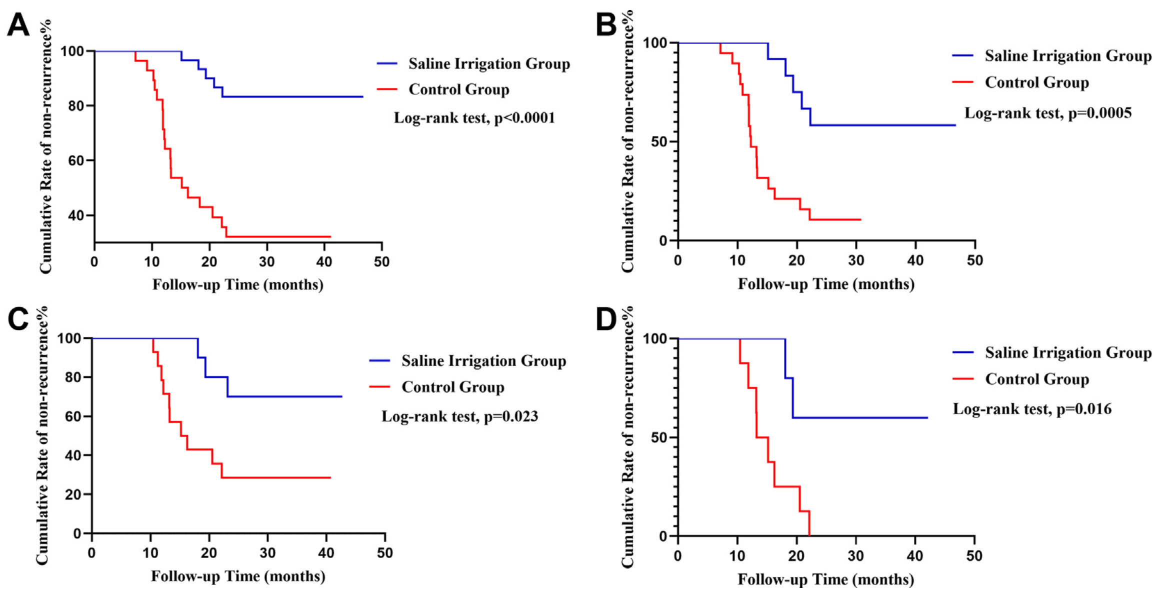

Fig. 3: **A.** Saline irrigation can reduce the recurrence rate of stones in patients with PAD; **B.** Saline irrigation can reduce the recurrence rate of stones in patients with intra diverticulum papillae; **C.** Saline irrigation can reduce the recurrence rate of stones in patients with constipation; **D.** Saline irrigation reduces the recurrence rate of stone in patients with constipation and diverticulum.

increased intestinal pressure, which increases duodenal-bile reflux.[30] The presence of PAD slows bile emptying and reduces the scouring effect of bile on the biliary tract. In addition, the remaining chyme in the diverticulum and the colonized bacteria often cause diverticulitis, which affects the function of the papilla.[27] The increased intestinal pressure makes the diverticulitis contents containing bacteria flow back into the biliary tract with intestinal fluid to induce inflammation and stone formation.[27,29] If there are residual stone fragments in the biliary tract, which become the basis of stone formation, multiple factors increase the probability of stone recurrence. Therefore, for stone patients with constipation, biliary saline irrigation after ERCP combined with regular defecation may reduce stone recurrence.

There were several strengths in this clinical study. First, MRCP was used to diagnose choledocholithiasis during the follow-up period, which improved the diagnostic accuracy. Second, the new classification of PAD and constipation were introduced as observation indicators. Finally, this trial was the first prospective randomized controlled study of the association between saline irrigation and stone recurrence after mechanical lithotripsy. In addition, although this study was a single-centre study, the results indicate that saline irrigation is a safe, effective, and easy-to-perform procedure with universal applicability.

There were also some limitations in our study. First, this study was a single-institution study, and the results may be more convincing if further multicenter clinical studies are conducted. Second, the number of patients with constipation was small. Our finding that constipation is a risk factor for stone recurrence after endoscopic lithotripsy and stone extraction should be verified by studies using a larger sample size.

In conclusion, for patients with CBDS requiring lithotripsy, 100 ml saline irrigation is an effective method to reduce stone recurrence after endoscopic stone removal. Given this method's efficiency, simplicity, low cost, and safety, saline irrigation is recommended as a routine operation procedure after endoscopic lithotripsy and stone extraction.

Contributors

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Data sharing statements

Except for the patients' privacy, some fields in data, the study protocol, statistical analysis plan, data dictionary and deidentified results of these analyses are available for scientific researchers upon reasonable request through the first or corresponding author. The data will be kept for three years after the publication of the article.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101978.

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