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Extracorporeal Shock-Wave Lithotripsy and Endoscopy for the Treatment of Pain in Chronic Pancreatitis

A Sham-Controlled, Randomized Trial

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Background: No randomized controlled trials have substantiated endoscopic decompression of the pancreatic duct in patients with painful chronic pancreatitis.

Objective: To investigate the pain-relieving effect of pancreatic duct decompression in patients with chronic pancreatitis and intraductal stones.

Design: 24-week, parallel-group, randomized controlled trial (ClinicalTrials.gov: NCT03966781)

Setting: Asian Institute of Gastroenterology in India from February 2021 to July 2022.

Participants: 106 patients with chronic pancreatitis.

Intervention: Combined extracorporeal shock-wave lithotripsy (ESWL) and endoscopic retrograde pancreatography (ERP) compared with sham procedures.

Measurements: The primary end point was pain relief on a 0- to 10-point visual analog scale (VAS) at 12 weeks. Secondary outcomes were assessed after 12 and 24 weeks and included 30% pain relief, opioid use, pain-free days, questionaries, and complications to interventions.

Results: 52 patients in the ESWL/ERP group and 54 in the sham group were included. At 12 weeks, the ESWL/ERP group showed better pain relief compared with the sham group (mean difference in change, −0.7 [95% CI, −1.3 to 0] on the VAS; $P = 0.039$). The difference between groups was not sustained at the 24-week follow-up, and no differences were seen for 30% pain relief at 12- or 24-week follow-up. The number of pain-free days was increased (median difference, 16.2 days [CI, 3.9 to 28.5 days]), and the number of days using opioids was reduced (median difference, −5.4 days [CI, −9.9 to −0.9 days]) in the ESWL/ERP group compared with the sham group at 12-week follow-up. Safety outcomes were similar between groups.

Limitation: Single-center study and limited duration of follow-up.

Conclusion: In patients with chronic pancreatitis and intraductal stones, ESWL with ERP provided modest short-term pain relief.

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Pain is a major challenge in chronic pancreatitis and is often associated with pancreatic duct obstruction due to stones and/or strictures. Endoscopic interventions, often in combination with extracorporeal shock-wave lithotripsy (ESWL), aim to alleviate this pain by decompressing the pancreatic duct (1). However, the precise relationship between pain and pancreatic duct morphology remains elusive, and the existing evidence on the effectiveness of these interventions primarily relies on observational studies and procedural comparisons (2–5). Furthermore, it is well established that invasive interventions for pain-associated conditions, including surgery and endoscopic therapy, can elicit substantial sham effects (6). Consequently, there is a clear need for rigorously designed randomized trials incorporating a sham group to comprehensively evaluate the efficacy and safety of such interventions. To address this knowledge gap, we initiated the SCHOKE (Extracorporeal Shock Wave Lithotripsy and Endotherapy for Pain in Chronic Pancreatitis) trial to assess the pain-relieving effect and safety of pancreatic duct decompression using ESWL and endoscopic retrograde pancreatography (ERP) compared with sham procedures.

Methods

Trial Design and Oversight

This was a single-center, single-blinded, parallel-group, randomized, sham-controlled, superiority trial. The Study Protocol (available at Annals.org) followed the SPIRIT (Standard Protocol Items: Recommendations

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for Interventional Trials) guidelines and the principles of the Declaration of Helsinki. The Study Protocol has been published previously (7). An independent data and safety monitoring board oversaw the trial and comprised a neurologist, an anesthesiologist, and a statistician.

Trial Population and Setting

We assessed consecutive patients (≥18 years old of both sexes) attending the Pancreas Clinic of the study center with definite chronic pancreatitis according to the Mayo Clinic criteria (requiring either pancreatic calcifications, Cambridge III/IV pancreatic duct abnormalities, or histologic confirmation) for inclusion between 1 February 2021 and 31 July 2022 (8). Patients who had chronic abdominal pain characteristic of chronic pancreatitis with a pain intensity greater than 3 on a 0 to 10 visual analog scale (VAS), who met the criteria for chronic pain (pain ≥3 days per week for ≥3 months), and had obstruction of the pancreatic duct due to intraductal stones with dilation of the duct proximal to the obstruction were included. Pancreatic ductal dilatation and the presence of intraductal stones were assessed using either magnetic resonance cholangiopancreatography or abdominal computed tomography. We excluded patients with previous pancreatic surgery, ESWL, or endoscopic therapy directed at the pancreatic duct. Also, patients with multiple pancreatic duct strictures, pancreas mass lesions, large ascites, and large pancreatic or peripancreatic fluid collections were excluded. Further details of inclusion and exclusion criteria are provided in the Supplement (available at Annals.org).

The study was conducted at the Asian Institute of Gastroenterology (Hyderabad, India), which is a large tertiary care referral center that serves patients across India and neighboring countries. Two members of the study team initially screened potential patients for eligibility in the pancreas clinic. Once enrolled and randomly assigned, the ESWL procedures were performed by 2 dedicated physicians aided by 1 dedicated anesthesiologist who administered the epidural anesthesia. The ERP procedures were performed by 4 advanced endoscopists who all had a minimum of 10 years of experience.

Procedures

Patients were randomly assigned in a 1:1 ratio to receive either combined ESWL and ERP or sham treatment. The allocation was concealed using an automatic assignment system. We used block randomization with groups of 6 patients per block, ensuring an equal distribution between the sham and ESWL/ERP procedures. The random assignment process was carried out by a physician who did not have access to the patient's clinical data.

In the ESWL/ERP group, ESWL was performed with the patient under epidural ropivacaine anesthesia, targeting the pancreatic stones. The patient's eyes were lightly covered during the procedure. After achieving epidural anesthesia, ESWL was conducted using a third-generation Dornier dual-focus lithotripsy system (Dornier Delta 3; Dornier MedTech GmbH), delivering a maximum of 5000 shocks at a rate of 90 shocks per minute. If complete stone fragmentation was not achieved during the initial ESWL session, additional sessions were scheduled on subsequent days. Complete stone fragmentation was defined as the fragmentation of all stones to 3 mm or less (1). The day after lithotripsy, stone fragments were removed during an ERP procedure. This involved pancreatic sphincterotomy and stone removal with verification of pancreatic duct clearance. Complete pancreatic duct clearance was defined as a more than 90% reduction in the initial stone volume based on the fluoroscopic view of the stone density during the ESWL and subsequent ERP procedure (9). During ERP, in cases where cannulation failed after a maximum of 5 attempts, a precut pancreatic sphincterotomy was performed. If a pancreatic duct stricture was identified during the ERP procedure, the stricture was dilated if needed before pancreatic duct stent placement. A single plastic pancreatic stent (diameter, 5 to 7 Fr; length, 7 to 10 cm) was inserted in all patients in the ESWL/ERP group per our clinical routine practice. A follow-up ERP procedure after 6 months was scheduled for stent exchange or removal after completion of all study assessments.

In the sham group, patients experienced a superficial pinprick sensation with a sterile hypodermic needle without penetrating the skin to mimic the sensation of epidural anesthesia before the sham ESWL procedure. After this, the lithotripsy machine was activated without making any physical contact with the patient's body. Throughout the entire procedure, the patient's eyes were gently covered. Subsequently, after the sham ESWL, patients had a sham ERP procedure, which involved the intubation of the duodenum with an upper gastrointestinal endoscope without any contact with the papillary area and pancreatic duct interventions.

Patients were observed in the endoscopy recovery area for 6 to 12 hours after the procedures. If the patients had abdominal pain during the observation period, serum lipase was evaluated to identify post-procedure pancreatitis.

Patients were advised to maintain their usual medical treatment, including antioxidants and pancreatic enzyme supplements, throughout the trial. Pain management was documented at the screening visit and the 12- and 24-week follow-ups. In addition, patients were permitted to use rescue pain medication in the form of nonsteroid anti-inflammatory drugs or opiates during the trial and were required to record its type and usage in the pain diary.

End Points

The study personnel assessing the treatment outcomes were not aware of the treatment allocation. Average daily clinical pain-intensity scores were recorded in a patient pain diary based on a 0 to 10 VAS, with the registration of the baseline pain-intensity scores from the

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week before intervention and weekly recordings continued for a 24-week period after intervention. Mean values of pain scores were calculated over each week to adjust for day-to-day variability in pain intensity. We compared the change from baseline in the mean pain score between groups over the course of the study, with the primary end point being the difference between groups after 12 weeks. Weekly telephone interviews with a study coordinator were undertaken to facilitate accurate registration and adherence to registering pain scores.

Prespecified secondary end points were assessed at 12 and 24 weeks of follow-up and included: i) partial pain relief (defined by a decrease in the pain-diary score [VAS] of 30% compared with baseline), ii) the number of pain-free days during follow-up, iii) the cumulative use of opioid-based analgesics (days using opioids), iv) hospitalization during follow-up, and v) group differences in changes from baseline for patient-reported outcomes including pain-diary score at 24-week follow-up, quality of life (the EORTC Quality of Life questionnaire), and composite pain severity and interference scores of the Brief Pain Inventory–Short Form questionnaire. In addition, proportions of patients with depression and anxiety (the Hospital Anxiety and Depression Scale) and patients with much or very much improved health status (Patient Global Impression of Change [PGIC] questionnaire) were compared between groups at 12- and 24-week follow-up. A detailed description of the questionnaires is provided in the **Supplement**.

The Study Protocol prespecified all primary and secondary end points. Three secondary end points (days using opioids, hospitalization, and presence of anxiety and depression) were redefined during our data analysis (**Supplement Table 1**, available at Annals.org). Information on the procedures used for preprocessing data before analysis is provided in **Supplement Table 2** (available at Annals.org).

Safety end points included postprocedure acute pancreatitis according to the modified Atlanta criteria (10), perforation, bleeding, and infections (definitions provided in the **Supplement**).

Statistical Analysis

The study was powered to detect a minimal difference between groups in the change in weekly pain-diary scores at 12 weeks of 30%. We assumed a baseline pain-diary score of 5 on the 0 to 10 VAS and anticipated a 20% response in the sham group, resulting in a decrease in pain score from 5 to 4 on the VAS and a further 30% reduction in the ESWL/ERP group, leading to a VAS score of 2.8 (11). This corresponds to a group difference of 1.2 on the VAS. Based on an assumed SD of 45%, we determined that a study with 48 patients per group was needed to provide a power of 90% using a 2-sided significance level of 0.05 (12). To allow for a 10% dropout, the sample size was set at 106 patients. A prespecified interim analysis was conducted after 45 patients had been randomly assigned and completed 24 weeks of follow-up (7). No statistically significant differences were seen between groups (**Supplement Figure**, available at Annals.org), and the data and safety monitoring board recommended continuing and completing the trial.

The intention-to-treat population included all of the patients who were randomly assigned, and the trial data were analyzed according to the intention-to-treat principle. Categorical variables are reported as counts and percentages, and continuous variables as means with SD or medians with IQRs. A repeated measures, linear, mixed-effect model was used to analyze the primary outcome, and summary statistics of mean pain scores (VAS) were provided for the individual

Table 1. Baseline Characteristics of Patients in the Intention-to-Treat Population

Patient Characteristic	ESWL/ERP (*n* = 52)	Sham (*n* = 54)
Male sex, *n (%)*	37 (71)	39 (72)
Mean age (SD), *y*	37.2 (11.6)	38.2 (12.1)
Age group, *n (%)*		
<30 y	16 (31)	13 (24)
30–39 y	17 (33)	19 (35)
40–49 y	10 (19)	12 (22)
50–59 y	8 (15)	6 (11)
≥60 y	1 (2)	4 (7)
Cause of pancreatitis, *n (%)**		
Alcohol	17 (33)	20 (37)
Idiopathic	30 (58)	30 (56)
Other	5 (10)	4 (7)
Current smoking, *n (%)*	13 (25)	9 (17)
Diabetes, *n (%)*	21 (40)	21 (39)
Analgesics, *n (%)*		
None	9 (17)	6 (11)
Mild	17 (33)	22 (41)
Strong (opioids)†	26 (50)	26 (48)
Mean pancreatic duct diameter (SD), *mm*	8.0 (3.3)	7.5 (2.9)
Pancreatic duct calculi, *n (%)*		
Single	21 (40)	21 (39)
Multiple	31 (60)	33 (61)
Pancreatic duct calculi location, *n (%)*		
Head	30 (58)	34 (63)
Genu	1 (2)	0 (0)
Neck	2 (4)	1 (2)
Proximal body	7 (14)	3 (6)
Multiple sites	12 (23)	16 (30)
Mean diameter of largest calculus (SD), *mm*	9.8 (3.8)	10.5 (4.2)
Pancreatic duct stricture, *n (%)*‡	4 (8)	3 (6)
Parenchymal calcification(s), *n (%)*	30 (58)	39 (72)

ERP = endoscopic retrograde pancreatography; ESWL = extracorporeal shock-wave lithotripsy.

* In the ESWL/ERP group, of the 17 patients who were assigned an alcohol-related cause of pancreatitis, 10 also smoked cigarettes. In addition, 3 patients only smoked. These 3 patients have been categorized under "Other causes of pancreatitis." In the sham group, of the 20 patients who were assigned an alcohol-related cause of pancreatitis, 8 also smoked cigarettes. In addition, 1 patient only smoked. This patient has been categorized under "Other causes of pancreatitis."

† None of the patients included in the study were on long-term opioid therapy, and most of the opioids taken were of low potency (tramadol) and were taken on an as-needed basis.

‡ All strictures were single, short, and located in the pancreatic head region. In 3 patients from the ESWL/ERP group, the stricture was only detected during ERP. None of the strictures were tight, and they could be managed with a pancreatic duct stent without requiring further dilation.

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Table 2. Change From Baseline in Primary and Secondary End Points at 12 and 24 Weeks After Intervention

End Points	ESWL + ERP ($n = 52$)	Sham ($n = 54$)	Estimated Mean Difference From Baseline (95% CI)		
			ESWL/ERP	Sham	Mean Difference in Change
Pain diary					
Mean weekly pain score, VAS (SD)					
Baseline	5.6 (1.4)	5.7 (1.1)	–	–	–
Week 12	0.6 (1.1)	1.5 (1.5)	−5.0 (−5.4 to −4.5)	−4.3 (−4.7 to −3.8)	−0.7 (−1.3 to 0)*
Week 24	0.4 (1.3)	1.3 (2.0)	−5.3 (−5.8 to −4.7)	−4.5 (−5.1 to −3.8)	−0.8 (−1.6 to 0.1)
Brief Pain Inventory					
Mean pain intensity score, NRS (SD)					
Baseline	3.9 (1.9)	3.3 (1.7)	–	–	–
Week 12	0.3 (0.8)	1.2 (1.5)	−3.6 (−4.2 to −3.0)	−2.1 (−2.6 to −1.6)	−1.5 (−2.3 to −0.7)
Week 24	0.4 (1.1)	0.9 (1.8)	−3.5 (−4.2 to −2.9)	−2.4 (−3.1 to −1.7)	−1.2 (−2.1 to −0.2)
Mean pain interference score, NRS (SD)					
Baseline	1.1 (1.0)	1.6 (1.3)	–	–	–
Week 12	0.4 (0.8)	0.9 (1.0)	−0.7 (−1.0 to −0.3)	−0.6 (−1.0 to −0.2)	0 (−0.6 to 0.5)
Week 24	0.3 (0.7)	0.5 (0.8)	−0.8 (−1.2 to −0.5)	−1.1 (−1.5 to −0.7)	0.2 (−0.3 to 0.8)
EORTC QLQ-C30					
Mean global health status score (SD)					
Baseline	52.7 (21.4)	49.8 (15.2)	–	–	–
Week 12	68.2 (24.5)	62.9 (19.0)	15.5 (6.8 to 24.2)	13.0 (6.8 to 19.2)	2.5 (−8.3 to 13.3)
Week 24	70.0 (24.8)	71.1 (18.9)	17.2 (9.6 to 24.9)	21.3 (15.4 to 27.2)	−4.0 (−13.7 to 5.6)
Mean physical functioning score (SD)					
Baseline	82.7 (19.3)	83.1 (19.7)	–	–	–
Week 12	84.3 (17.9)	81.1 (18.5)	1.6 (−4.1 to 7.3)	−1.9 (−7.2 to 3.3)	3.5 (−4.3 to 11.4)
Week 24	89.1 (14.8)	87.3 (13.2)	6.4 (0.9 to 12.0)	4.2 (−1.7 to 10.1)	2.2 (−6.0 to 10.4)
Mean role functioning score (SD)					
Baseline	77.6 (30.2)	72.2 (27.9)	–	–	–
Week 12	82.4 (25.0)	77.9 (26.8)	4.9 (−4.6 to 14.3)	5.7 (−3.1 to 14.5)	−0.9 (−13.8 to 12.1)
Week 24	82.3 (27.3)	86.6 (19.3)	4.7 (−4.8 to 14.3)	14.4 (7.1 to 21.7)	−9.6 (−21.6 to 2.3)
Mean emotional functioning score (SD)					
Baseline	60.7 (27.9)	62.7 (20.5)	–	–	–
Week 12	72.9 (23.0)	70.4 (19.9)	12.1 (3.1 to 21.2)	7.8 (2.6 to 13.0)	4.4 (−5.9 to 14.7)
Week 24	71.8 (25.9)	83.1 (16.2)	11.1 (2.8 to 19.3)	20.4 (13.8 to 27.0)	−9.3 (−20.1 to 1.4)
Mean cognitive functioning score (SD)					
Baseline	87.8 (16.5)	79.6 (19.9)	–	–	–
Week 12	84.0 (20.0)	85.1 (17.9)	−3.8 (−10.1 to 2.6)	5.4 (−0.4 to 11.2)	−9.2 (−17.8 to −0.1)
Week 24	88.7 (17.1)	92.9 (14.1)	1.0 (−5.2 to 7.3)	13.3 (7.6 to 19.0)	− 12.2 (−20.7 to −3.8)
Mean social functioning score (SD)					
Baseline	85.9 (22.7)	84.0 (21.2)	–	–	–
Week 12	86.8 (23.7)	81.6 (23.4)	0.9 (−7.0 to 8.9)	−2.4 (−9.5 to 4.7)	3.3 (−7.5 to 14.1)
Week 24	85.8 (23.7)	90.5 (14.6)	−0.1 (−7.2 to 7.0)	6.6 (0 to 13.2)	−6.7 (−16.3 to 2.9)

EORTC QLQ-C30 = EORTC Quality of Life Core Questionnaire; ERP = endoscopic retrograde pancreatography; ESWL = extracorporeal shock-wave lithotripsy; NRS = numerical rating scale; VAS = visual analog scale.
* Primary end point; $P = 0.039$.

time points with corresponding 95% CIs. Secondary outcomes were analyzed using mixed-effect models (as for the primary end point), quantile regression models, and risk differences. Variables with missing values were analyzed after implementing the multiple-imputation technique. A 2-sided *P* value of less than 0.049 was considered to indicate statistical significance for the primary end point (to account for the interim analysis). Additional information on the statistical methods is provided in the **Supplement**. All analyses were done using STATA version 17.0 (StataCorp).

Role of the Funding Source

The study was supported by our institutions. The funders had no influence on the study design, data collection, statistical analysis, preparation of the manuscript, or the decision to publish.

RESULTS

Participants

Between 1 February 2021 and 31 July 2022, a total of 388 patients with chronic pancreatitis were assessed for eligibility. In total, 106 patients were randomly assigned to the ESWL/ERP group ($n = 52$) or the sham group ($n = 54$) and were included in the primary analysis (**Appendix Figure**, available at Annals.org). Characteristics of the patients at baseline were evenly distributed between the 2 trial groups (**Table 1**). Due to unbearable pain that either persisted or increased after the intervention, ESWL/ERP was done in 2 patients in the sham group during the initial 12-week follow-up and in 1 additional patient between 12- and 24-week follow-up (**Appendix Figure**).

Patients randomly assigned to the ESWL/ERP group received a median of 5000 shocks (IQR, 800). Among

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them, 32 patients (62%) achieved complete stone fragmentation during the initial ESWL session, 17 (33%) required 2 sessions, and 3 (6%) required 3 sessions to achieve complete stone fragmentation. All patients in the ESWL/ERP group had a single ERP procedure to clear the pancreatic stone fragments. Complete pancreatic ductal clearance was accomplished in 46 patients (88%). In 2 patients, ERP was not feasible due to duodenal edema; no further ERP attempts were made in these patients. In addition, 4 patients had incomplete ductal clearance because of a pancreatic duct stricture. A pancreatic duct stent was successfully placed in all patients having ERP without the need for stricture dilation. During follow-up, pancreatic stent migration was seen in 7 patients (14%) who had a stent inserted at baseline in the ESWL/ERP group. Patients with stent migration did not undergo an ERP procedure after 24 weeks of follow-up.

Clinical Outcomes After 12-Week Follow-up

The primary and secondary end points after 12-week follow-up are reported in Tables 2 and 3. The mean change from baseline in the pain-diary score (VAS) after 12 weeks of follow-up was −5.0 (95% CI, −5.4 to −4.5) in the ESWL/ERP group and −4.3 (CI, −4.7 to −3.8) in the sham group (mean difference, −0.7 [CI, −1.3 to 0]; $P = 0.039$) (Figure 1, *top*). In the ESWL/ERP group, 98% of patients reported partial pain relief after 12 weeks compared with 91% in the sham group (risk difference, 7% [CI, −1% to 16%]) (Figure 1, *bottom*). The median number of days without pain was 58.2 days in the ESWL/ERP group and 42.0 days in the sham group (median difference, 16.2 days [CI, 3.9 to 28.5 days]). The median cumulative number of days using opioids was 4.6 in the ESWL/ERP group and 10.0 in the sham group (median difference, −5.4 days [CI, −9.9 to −0.9 days]) (Figure 2). During the 12-week postintervention period, 28% of patients in the ESWL/ERP group had 1 or more hospital contacts compared with 38% of patients in the sham group (risk difference, −10% [CI, −28% to 8%]).

The mean change from baseline in the Modified Brief Pain Inventory–Short Form pain severity score (numeric rating scale) after 12 weeks of follow-up was −3.6 (CI, −4.2 to −3.0) in the ESWL/ERP group and −2.1 (CI, −2.6 to −1.6) in the sham group (mean difference, −1.5 [CI, −2.3 to −0.7]). The proportion of patients with a Hospital Anxiety and Depression score greater than 7 points (indicative of depression) was 17% in the ESWL/ERP group and 35% in the sham group at 12 weeks (risk difference, −18% [CI, −34% to −2%]). In the ESWL/ERP group, 71% of patients reported much or very much improved health status after 12 weeks compared with 46% in the sham group (risk difference, 25% [95% CI, 7% to 43%]). There were

Table 3. Summary Results of Secondary End Points at 12 and 24 Weeks After Intervention

Secondary End Points	ESWL/ERP ($n = 52$)	Sham ($n = 54$)	Mean Group Difference (95% CI)
Responders to intervention, *n (%)**			
12 wk	51 (98)	49 (91)	7 (−1 to 16)
24 wk	51 (98)	49 (91)	7 (−1 to 16)
Median pain-free days (IQR), *n*			
12 wk	58.2 (28.0)	42.0 (37.0)	16.2 (3.9 to 28.5)
24 wk	130.0 (34.8)	99.6 (84.0)	30.4 (8.6 to 52.2)
Median days using opioids (IQR), *n*			
12 wk	4.6 (7.0)	10.0 (14.0)	−5.4 (−9.9 to −0.9)
24 wk	6.4 (9.0)	15.0 (22.0)	−8.6 (−14.7 to −2.5)
Hospitalization, *n/N (%)*			
12 wk	14/49 (29)	20/52 (38)	−10 (−28 to 8)
24 wk	16/49 (33)	25/52 (48)	−15 (−34 to 3)
Anxiety, *n (%)*†			
12 wk	16 (31)	19 (35)	−4 (−22 to 13)
24 wk	6 (11)	4 (7)	4 (−7 to 15)
Depression, *n (%)*†			
12 wk	9 (17)	19 (35)	−18 (−34 to −2)
24 wk	6 (12)	3 (6)	6 (−5 to 17)
Patient Global Impression of Change, *n (%)*‡			
12 wk	37 (71)	25 (46)	25 (7 to 43)
24 wk	40 (77)	34 (63)	14 (−3 to 31)

ERP = endoscopic retrograde pancreatography; ESWL = extracorporeal shock-wave lithotripsy.
* A responder was defined as a person with a 30% or more reduction in the pain-diary score between baseline and 12- and 24-wk follow-up. A similar proportion of responders was observed at 12- and 24-wk follow-up in both groups.
† Scores greater than 7 on the Hospital Anxiety and Depression Scale subscales were considered as signs of anxiety and depression, respectively.
‡ The numbers (percents) of patients with much or very much improved health status are reported.

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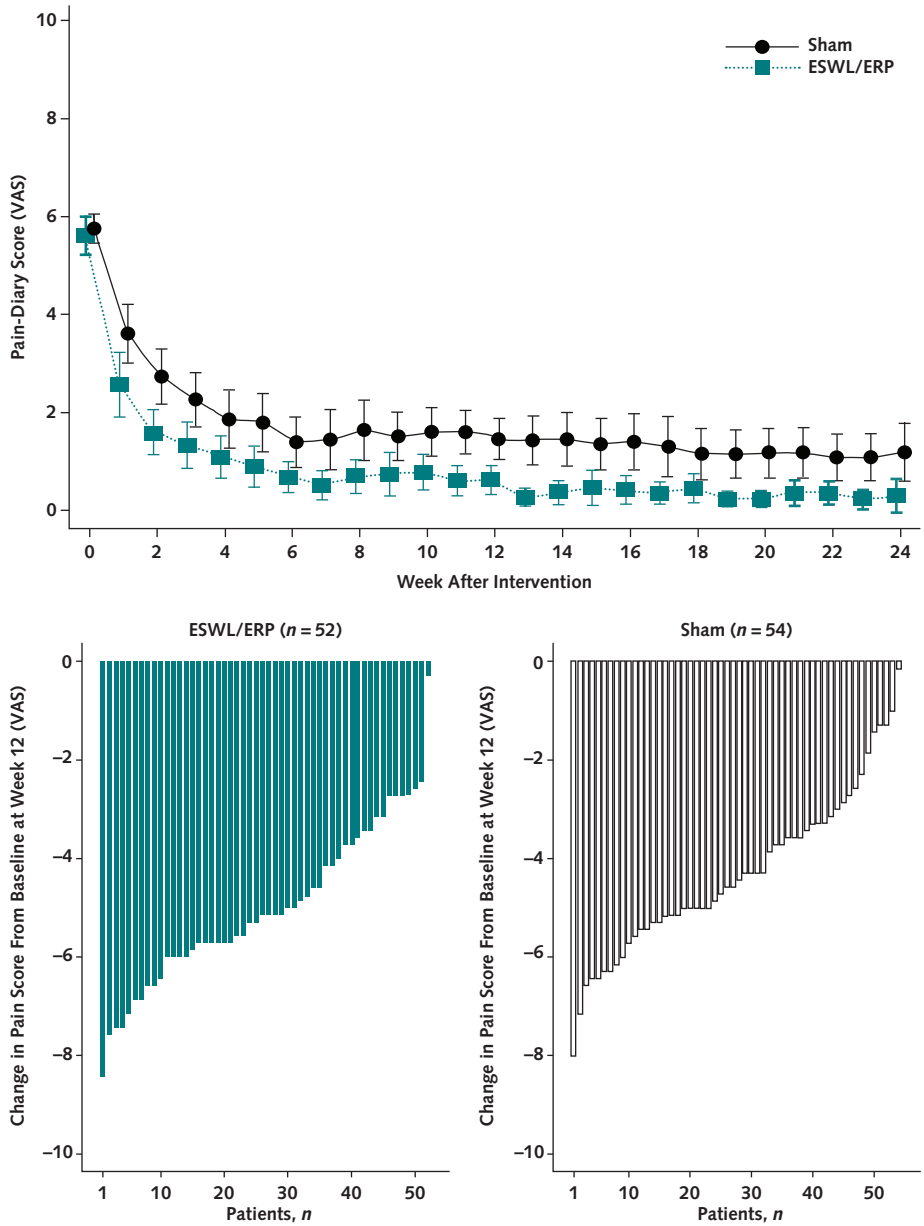
Figure 1. Pain-diary scores in patients having ESWL/ERP and sham.



ERP = endoscopic retrograde pancreatography; ESWL = extracorporeal shock-wave lithotripsy; VAS = visual analog scale.
Top. Pain-diary scores (VAS) for 24-week follow-up in patients having ESWL/ERP and sham. **Bottom.** Change in pain scores from baseline at 12-week follow-up in patients having ESWL/ERP and sham.

no clinically significant differences between the 2 groups in relation to mean change from baseline in the EORTC QLQ-C-30 global health status or functional scores (**Figure 3**) or the remaining secondary end points after 12 weeks (**Tables 2** and **3**).

Supplement Table 3 (available at Annals.org) provides the results of the complete case analyses of the mean change from baseline in the pain-diary score (VAS) after 12 and 24 weeks. This analysis showed literally the same results as reported for the primary analysis of imputed data.

Clinical Outcomes After 24-Week Follow-up

The mean change from baseline in the weekly pain-diary score (VAS) after 24 weeks of follow-up was −5.3 (CI, −5.8 to −4.7) in the ESWL/ERP group and −4.5 (CI, −5.1 to −3.8) in the sham group (mean difference, −0.8 [CI, −1.6 to 0.1]). The median number of pain-free days was increased, and the median number of days using opioids was reduced in the ESWL/ERP group. Otherwise, no differences between the 2 groups were seen for the remaining end points after 24 weeks (**Tables 2** and **3**).

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Safety Outcomes

Table 4 reports the safety outcomes. The frequency of postprocedure acute pancreatitis was comparable between groups (risk difference, 4% [CI, −3% to 11%]), and none of the other prespecified complications from study interventions were seen.

Discussion

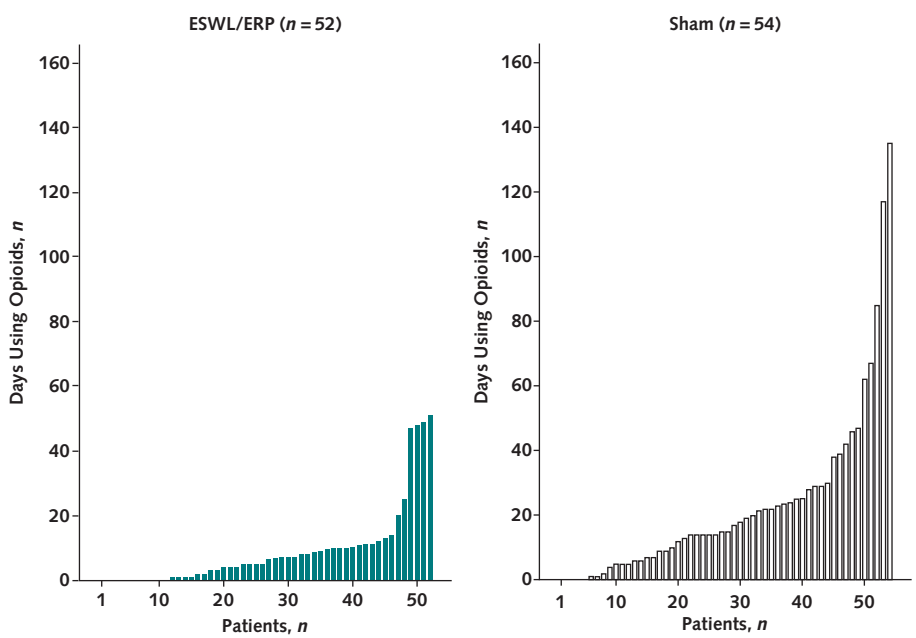
This study, to our knowledge, is the first randomized controlled trial to examine the effect of ESWL/ERP versus sham intervention on pain relief in patients with chronic pancreatitis and pancreatic duct obstruction. We found that the ESWL/ERP group experienced a modest reduction in pain in the short-term compared with the sham group. This improvement was accompanied by a decrease in the use of opioid-based analgesics, lower levels of depression, and overall better-perceived health status after a 12-week follow-up. However, the difference between groups was not sustained at the 24-week follow-up.

Abdominal pain is present in up to 80% of patients with chronic pancreatitis (13). When analgesic treatment is insufficient, and pancreatic duct obstruction is suspected from imaging, first-line therapy is endoscopic decompression (or, in some cases, surgery). However, the rationale for endoscopic treatment of pain associated with pancreatic duct obstruction has been disputed because parenchymal/ductal pressure or imaging findings relate poorly to symptoms (14, 15). On the other hand, observational studies have shown a major pain-relieving effect of ERP, especially when combined with ESWL (1), and, in a recent study, we showed that clinical evaluation suggestive of pancreatic duct obstruction, including imaging, correlated with pain severity scores (16). These contradictory findings were the rationale for the current sham-controlled trial.

The difference in pain relief between the groups in our study, measured at 0.7 points on the 0 to 10 VAS, indicates a modest level of pain relief (17). This raises questions about the clinical significance of the effect, especially given the invasive nature of the ESWL/ERP procedure and the associated risks for complications and costs. The small improvement in pain relief might be deemed insufficient for recommending this procedure widely to patients with painful chronic pancreatitis and an obstructed pancreatic duct. Despite the modest pain relief, there were notable improvements in secondary outcomes. These included reduced opioid use, lower prevalence of depression, and overall better-perceived health status among patients after 12 weeks. These findings suggest that pancreatic duct decompression could benefit some patients. Nonetheless, the effects seemed to diminish over time, as seen during the prolonged follow-up at 24 weeks.

The main reason for the improvements seen after pancreatic duct decompression is most likely the restoration of normal pancreatic juice flow and reduction of pancreatic duct pressure. Preclinical studies have shown that pancreatic duct hypertension produces inflammation via the mechanoreceptor Piezo1 expressed on pancreatic acinar cells (18). This, in turn, may lead to nociceptor activation in the pancreas and, thus, pain.

Figure 2. Number of days using opioids for 24-week follow-up in patients having ESWL/ERP and sham.



Each bar represents an individual patient. ERP = endoscopic retrograde pancreatography; ESWL = extracorporeal shock-wave lithotripsy.

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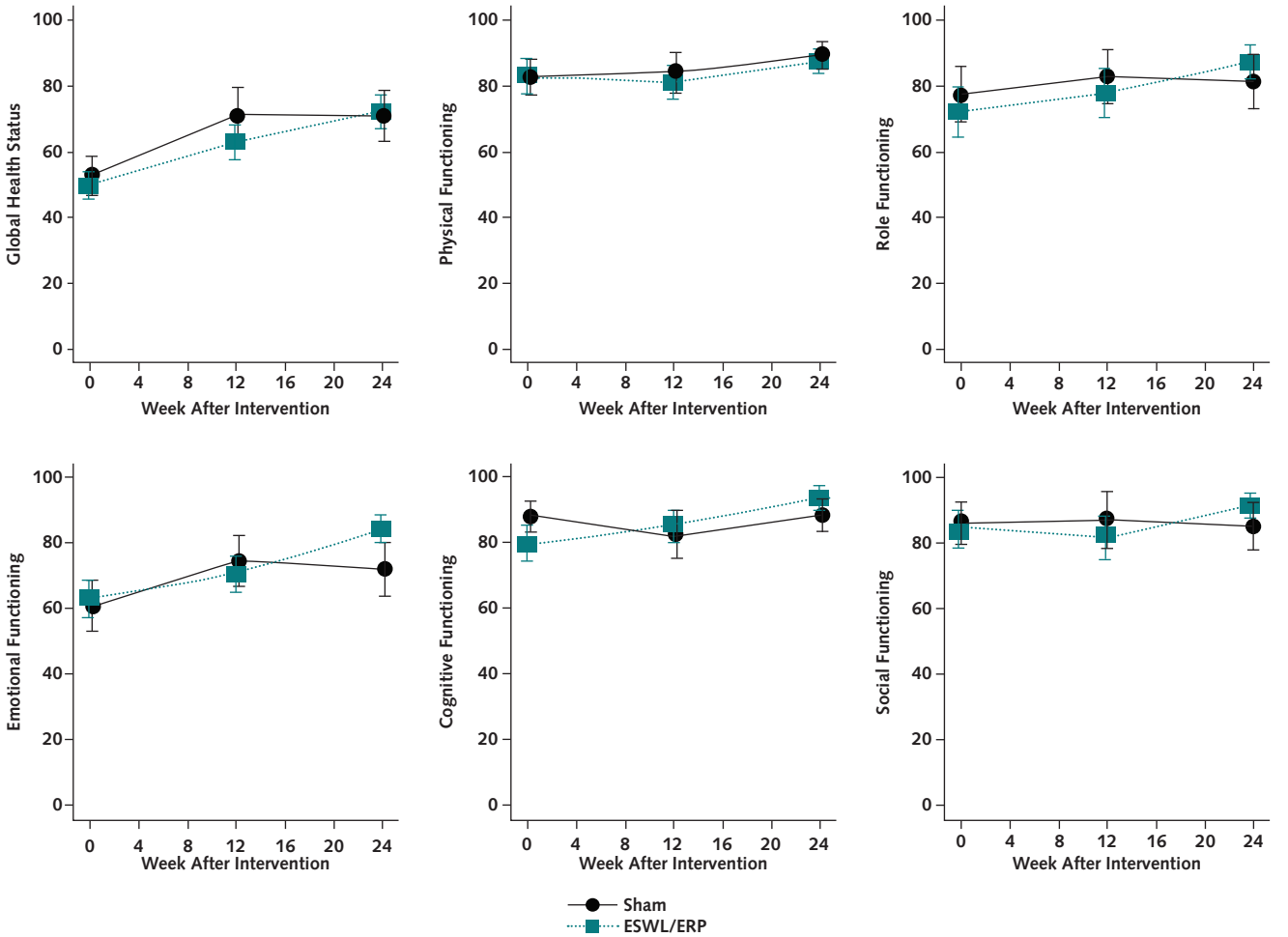
Figure 3. Global health status and functioning scores of the EORTC Quality of Life questionnaire in patients having ESWL/ERP and sham at baseline and 12- and 24-week follow-up.



Error bars are 95% CIs. ERP = endoscopic retrograde pancreatography; ESWL = extracorporeal shock-wave lithotripsy.

In addition to this nociceptive type of pain, patients with chronic pancreatitis often exhibit alterations in pain processing within central pain pathways (19). The nociceptive signals from primary afferent nerves originating in the pancreas may play a role in sustaining central neuronal sensitization (20), and pancreatic duct decompression could remove this source of central sensitization.

Significant pain reduction was seen in both treatment groups, with unexpected substantial and enduring pain relief noted in the sham group. However, ethical considerations allowed for the use of analgesics and optimized medical care. This may have contributed to the significant improvements seen in the sham group. Indeed, an increased number of days using opioids was seen in the sham group compared with the ESWL/ERP group. Moreover, previous studies on invasive treatments for chronic pain conditions have generally shown limited efficacy compared with sham interventions (21–24). Therefore, the substantial sham response seen in the present study underscores the importance of including a sham group when evaluating the efficacy of pain-relieving interventions (25).

A main limitation of the study was that a subset of patients, for practical reasons (among them the COVID-19 pandemic), had to fill out the pain diary and questionnaires remotely, and telephone consultations were used for follow-up. Another limitation was that a pain diary was used as the primary end point. This only measures the intensity of pain, whereas pain is normally regarded as a composite measure of affective and cognitive components, and instruments taking this into consideration may give a more precise measure of the effect (26). Also, our study was conducted at a single highly specialized center with substantial expertise in managing patients with chronic pancreatitis with pancreatic duct obstruction, which limits generalizability toward centers with less experience. This was highlighted by the higher pancreatic duct clearance rate seen in our study (88%) than in other studies. For example,

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Table 4. Summary Results of Safety Outcomes

Safety Outcomes	ESWL/ERP ($n = 52$)	Sham ($n = 54$)	Difference (95% CI)
Postprocedure acute pancreatitis, *n (%)**	3 (6)	1 (2)	4 (−3 to 11)
Endoscopic perforation, *n (%)*	0 (0)	0 (0)	–
Infection, *n (%)*	0 (0)	0 (0)	–
Bleeding after sphincterotomy, *n (%)*†	0 (0)	–	–

ERP = endoscopic retrograde pancreatography; ESWL = extracorporeal shock-wave lithotripsy.
* Acute pancreatitis was defined as a plasma lipase level >3 upper normal limits and abdominal pain within 12 hours of the procedure. According to the revised Atlanta criteria, all acute pancreatitis cases were classified as mild. Information on plasma lipase levels was missing for 1 patient.
† Sphincterotomy was not performed in the sham group.

a pancreatic duct clearance rate of 62% was reported in the ESCAPE (Effect of Early Surgery vs Endoscopy-First Approach on Pain in Patients with Chronic Pancreatitis) trial (5). Our study included patients who reported an average pain score of approximately 5 on the 0 to 10 VAS at baseline. Although this pain intensity corresponds to what is typically reported in observational and interventional studies of chronic pancreatitis (12, 16, 27), our findings may not be extrapolated to patients with more severe pain. Also, the relatively limited follow-up period of 24 weeks represents a limitation of our study, and future studies should aim to include longer follow-up periods. However, it may be difficult to maintain blinding in endoscopic studies over prolonged time periods due to the need for stent replacement or removal. Finally, the study population included only Indian patients. Compared with, for example, Western patients, an idiopathic cause was predominant, with only about 35% using excessive alcohol. It cannot be excluded that the effect of ESWL/ERP varies among diverse patient groups.

In conclusion, compared with a sham procedure, pancreatic ductal clearance using combined ESWL/ERP provided modest short-term pain relief in patients with chronic pancreatitis and intraductal stones.

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Note: Drs. Talukdar, Olesen, Reddy, and Drewes designed the trial. Drs. Talukdar and Olesen had access to the data, performed the analysis, and vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol.

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Data Sharing Statement: The following data will be made available with publication: Deidentified participant data. Restrictions: None. The Study Protocol is available in the **Supplement.** The statistical code used for the primary elements of analysis is provided in the **Supplement.** Further details are available from Dr. Olesen (soso@rn.dk). The data set is available upon reasonable request to the corresponding authors.

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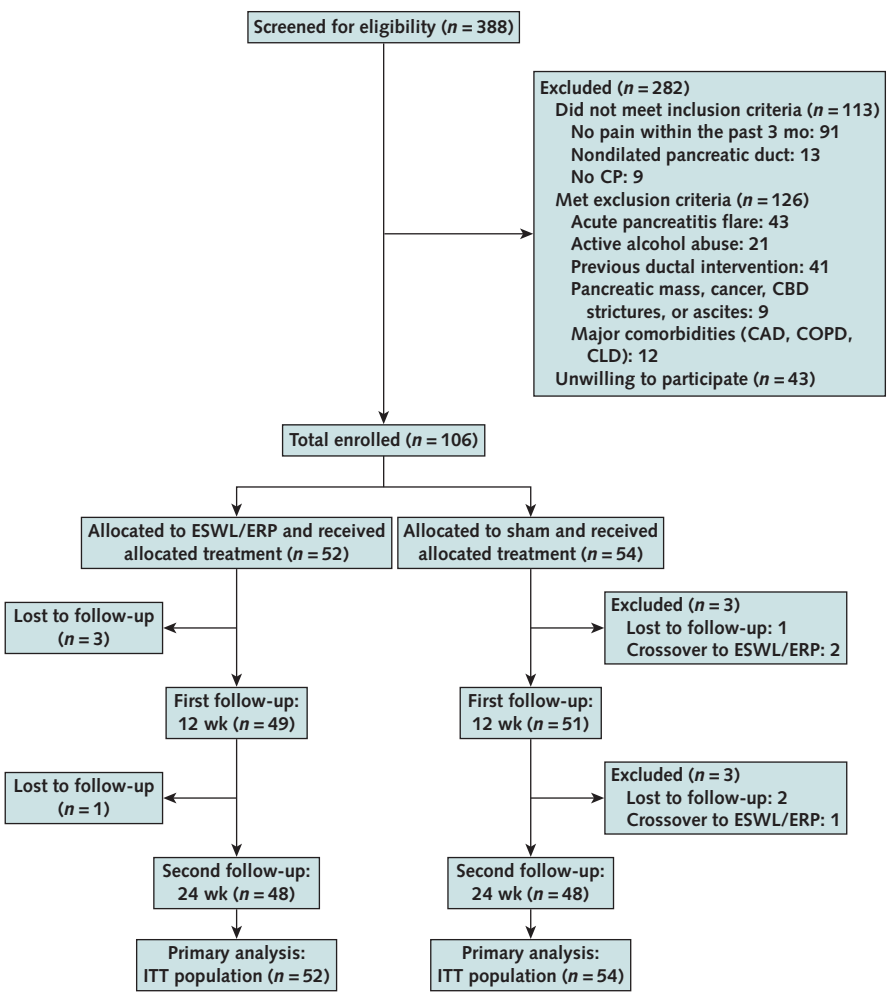
Appendix Figure. CONSORT flow diagram.



CAD = coronary artery disease; CBD = common bile duct; CLD = chronic liver disease; CONSORT = Consolidated Standards of Reporting Trials; COPD = chronic obstructive pulmonary disease; CP = chronic pancreatitis; ERP = endoscopic retrograde pancreatography; ESWL = extracorporeal shock-wave lithotripsy; ITT = intention to treat.

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