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ERCP with Extracorporeal Shock-Wave Lithotripsy For Chronic Pancreatitis: Is It A "Sham" for Improving Pain?

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This summary reviews Talukdar R, Olesen SS, Unnisa M et al. Extracorporeal Shock-Wave Lithotripsy and Endoscopy for the Treatment of Pain in Chronic Pancreatitis : A Sham-Controlled, Randomized Trial. Ann Intern Med. 2024 Jun;177(6):749-758.

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STRUCTURED ABSTRACT

Question: Is combined extracorporeal shock-wave lithotripsy (ESWL) and endoscopic retrograde cholangiopancreatography (ERCP) with pancreatic duct (PD) decompression superior to a sham procedure in alleviating pain in patients with chronic pancreatitis and intraductal stones?

Design: Single-center, parallel-group, sham-controlled, randomized controlled superiority trial with masking of patients and outcome assessors to intervention. Patients were enrolled from February 2021 to July 2022.

Setting: Pancreas Clinic of the Asian Institute of Gastroenterology (Hyderabad, India), a tertiary care referral center serving patients in India and neighboring countries. ESWL procedures were performed by 2 physicians, and ERCP by 4 advanced

endoscopists with a minimum of 10 years of experience.

Patients: Patients ages ≥18 years diagnosed with chronic pancreatitis, based on criteria including presence of pancreatic calcifications, Cambridge III/IV pancreatic duct abnormalities, or histologic confirmation of chronic pancreatitis, were included. Patients were required to have chronic abdominal pain consistent with chronic pancreatitis that occurred ≥3 days per week for ≥3 months, with a pain intensity >3 on a 0 to 10 visual analog scale (VAS). In addition, patients had PD obstruction due to intraductal stones with upstream PD dilation, determined using either magnetic resonance cholangiopancreatography (MRCP) or abdominal computed tomography. Notable exclusion criteria included prior pancreatic surgery, ESWL, or endoscopic therapy of the PD.

Interventions: Patients were randomly assigned in a 1:1 ratio to receive combined ESWL/ERCP vs. sham treatment. ESWL was performed under epidural anesthesia, with additional sessions if complete stone fragmentation was not achieved during the initial session. ERCP was then performed the day after lithotripsy to achieve PD clearance, defined as >90% reduction in the initial stone volume. A single plastic pancreatic stent was inserted in all patients in the ESWL/ERCP group. In comparison, the sham intervention consisted of a superficial pinprick sensation with a needle and the lithotripsy machine was then activated without making contact with the patient's body. To ensure masking of the patients, the patient's eyes were covered during both the ESWL and sham procedures. In the sham group, patients underwent a sham ERCP, where an endoscope was used to intubate the duodenum without any intervention.

Outcomes: Primary outcome was the mean change in pain score as assessed by the VAS at 12 weeks. This was assessed using a patient pain diary which recorded average and maximal daily pain intensity scores. There were multiple secondary outcomes assessed at 12- and 24-week follow-up, including change in pain score at 24 weeks, partial pain relief (30% improvement in VAS score compared to baseline), number of pain-free days, number of days using opioids, and hospitalization. Safety end points included post-procedure acute pancreatitis, perforation, bleeding, and infections.

Data Analysis: Intention-to-treat analysis was reported. For the primary outcome, a repeated measures, linear, mixed-effect model was used. An interim analysis was performed which showed no statistically significant difference between groups.

Two-sided p-value <0.049 was used as the threshold for statistical significance for the primary end point to account for the interim analysis.

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Results: Among 106 patients, 52 were randomized to the ESWL/ERCP group and 54 to the sham group. Mean age was 38 years, 72% of patients were male, 21% were current smokers, and 49% of patients were on strong opiates. Pancreatitis was attributed to alcohol in 35% of patients and idiopathic in 57%, and the mean diameter of the PD calculi was 10.2 mm. The mean baseline VAS pain score was 5.9 in the ESWL/ERCP group and 5.7 in the sham group. PD clearance was achieved in 46 (88%) patients in the ESWL/ERCP group.

Primary outcome: At 12 weeks, the mean change from baseline in VAS pain score was -5.0 (95% CI: -5.4 to -4.5) in the ESWL/ERCP group and -4.3 (95% CI: -4.7 to -3.8) in the sham group, resulting in a statistically significant mean difference in change in VAS of -0.7 (95% CI: -1.3 to 0; p=0.039). (Figure 1) However, at 24 week follow-up, there was no significant difference in VAS pain score between ESWL/ERCP group vs sham group: -5.3 (95% CI: -5.8 to -4.7) vs -4.5 (95% CI: -5.1 to -3.8), respectively, producing mean difference in change in VAS of -0.8 (95% CI: -1.6 to 0.1). (Figure 1) Also, there was no significant difference between groups for percentage of patients that achieved at least 30% pain relief from baseline at either 12 or 24 weeks.

There were numerical improvements in other secondary outcomes in the ESWL/ERCP vs. sham groups at 12 weeks, including partial pain relief (98% vs. 91%, risk difference: 7% [95 CI: 1% to 16%]), median number of pain-free days (58.2 vs. 42.0, median difference: 16.2 days [95% CI: 3.9 to 28.5]), number of days using opioids (4.6 vs. 10.0, median difference: 5.4 [95% CI: 9.9 to 0.9]), prevalence of depression (17% vs. 35%, risk difference: 18% [CI: 34% to 2%]), and self-report of improved health status (71% vs. 46%, risk difference: 25% [95% CI: 7% to 43%]). Post-procedure acute pancreatitis was numerically higher in ESWL/ERCP group vs sham group: 6% vs 2%, respectively.

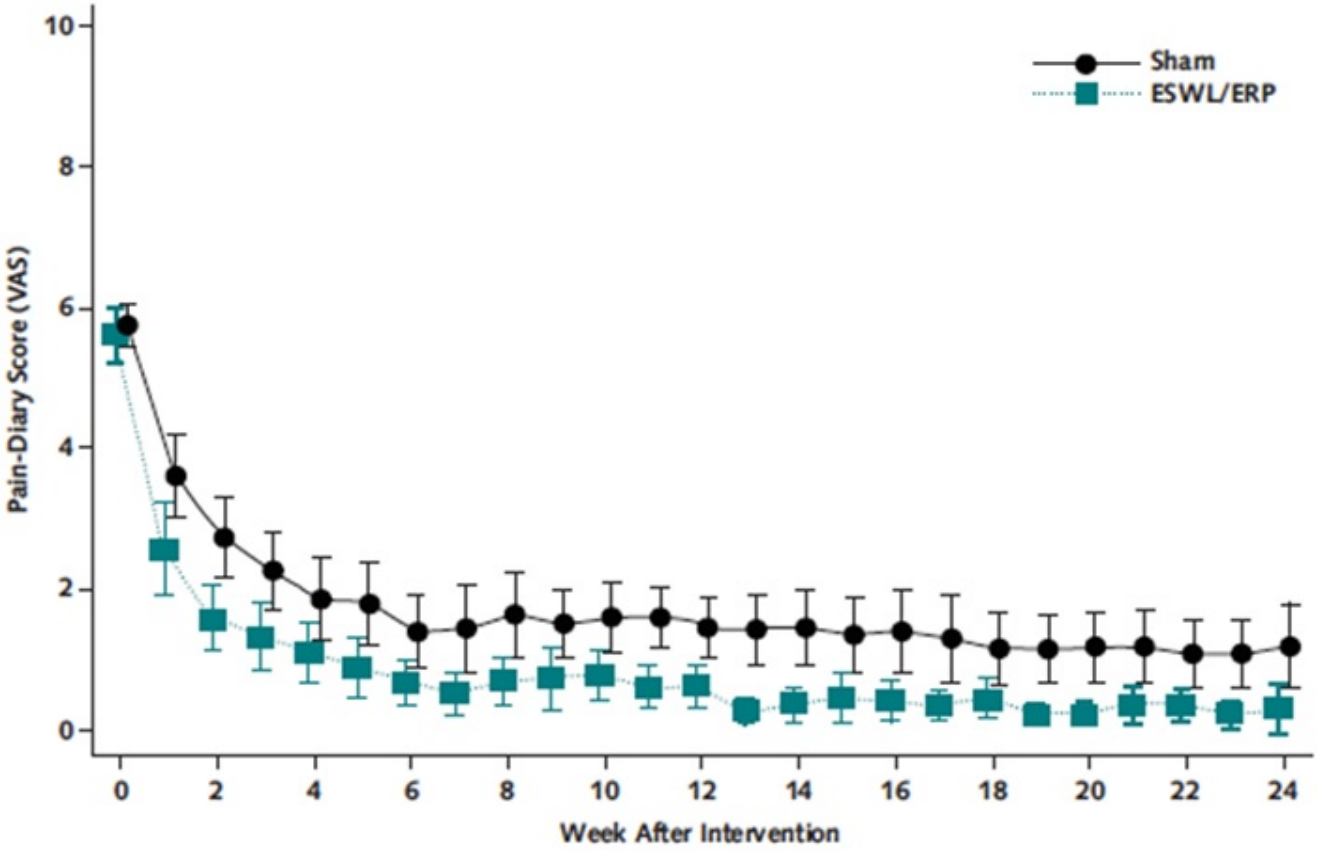

Figure 1. Visual analog scores for abdominal pain.

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COMMENTARY

Why Is This Important?

Abdominal pain significantly impacts quality of life and morbidity in patients with chronic pancreatitis, and up to 30% of patients will have PD obstruction.[1,2] Current guidelines support treatment of obstructive PD stones in patients with abdominal pain due to chronic pancreatitis, as PD obstruction may exacerbate pain. Most recently, the 2022 American Gastroenterological Association Clinical Practice Update supported use of ESWL and/or pancreatoscopy with intraductal lithotripsy for PD stones >5 mm and use of ERCP for clearance of ≤5 mm MPD stones.[3] Similarly, the 2018 ESGE Guidelines recommend ESWL for the clearance of radiopaque obstructive main PD stones ≥5 mm and ERCP for main PD stones that are radiolucent or <5 mm.[4]

Evidence to support these statements has relied mostly on small or observational studies, which have suggested

that combined ESWL/ERCP is effective in treating pain from chronic pancreatitis with obstructing PD stones.[5-7] A 2016 meta-analysis of 27 studies examining the use of ESWL (predominantly in combination with ERCP) in chronic pancreatitis with PD stones >5 mm reported complete ductal clearance in 71% of patients, absence of pain in 53% of patients at 2-year follow-up, and improved quality of life in 88% of patients, further supporting the potential efficacy of this therapy.[8] However, is the improvement in abdominal pain truly due to the efficacy of the procedure or is it due to the placebo response from an invasive intervention for chronic pain?

Invasive interventions for chronic pain frequently demonstrate efficacy in observational studies, but fail when compared to sham procedures.[9] Among advanced endoscopists, one of the best known examples is the EPISOD randomized controlled trial (RCT).[10] Prior to its publication in 2014, it was common to perform ERCP with sphincterotomy among post-cholecystectomy patients with persistent abdominal pain, which was thought to be due to Sphincter of Oddi (SOD) dysfunction. This approach was also supported by data from unblinded. observational retrospective studies. However, the blinded EPISOD RCT compared this intervention to ERCP without sphincterotomy. (Note: PD stent placement was performed in all patients to reduce post-ERCP pancreatitis when SOD manometry was performed.) Patients in both groups experienced major reductions or resolution of abdominal pain, but sphincterotomy provided no additional benefit. The excellent RCT by Talukdar and colleagues also produces similar outcomes.

Their study, entitled the SCHOKE RCT, is the first sham-controlled randomized trial investigating the use of ESWL/ERCP with PD decompression for the treatment of pain in chronic pancreatitis with obstructive PD stone(s). The use of a sham control group here is particularly impactful, as prior studies have suggested a strong placebo effect in patients with chronic pancreatitis, with reports of remission of abdominal pain in up to 20% of chronic pancreatitis patients treated with placebo tablets.[11] This study (SCHOKE RCT) also found large reductions in abdominal pain in both groups. (Figure 1) However, there was only a modest improvement in VAS pain scores at 12 weeks with ESWL/ERCP compared to sham. This met the threshold for statistical significance, but did not meet the pre-specified and generally accepted threshold for minimal clinically important difference. Furthermore, this effect did not persist at 24 weeks. Multiple secondary outcomes were assessed which suggested a numerical improvement or trend in rates of partial pain relief, pain-free days, days using opiates, as well as depression and self-reported quality of life scores.

Key Study Findings

Among patients with chronic abdominal pain due to chronic pancreatitis with obstructive PD stone(s), reduction in the

VAS pain score (on a scale from 0 to 10) was significantly greater in patients who underwent combined ESWL/ERCP vs. sham procedure: -5.0 vs. -4.3; mean difference -0.7 (95% CI: -1.3 to 0). Although this was a statistically significant difference, it did not meet criteria for a pre-specified and generally accepted threshold for minimal clinically important difference in pain reduction, and no significant improvement was demonstrated at 24 weeks, although both groups had large reductions in abdominal pain (Figure 1).

Caution

This was a single-center study performed at a specialized center with significant experience treating patients with chronic pancreatitis. Follow-up time for the primary outcome was only 12 weeks, and improvement in abdominal pain was seen in a high proportion of the sham-control group. It may be helpful to conduct further studies with larger study populations and longer term follow-up to assess the durability of outcomes of ESWL/ERCP. Lastly, ESWL for pancreatic lithiasis is not widely available in the US, where ERCP with electrohydraulic lithotripsy may be more common. Therefore, generalizability to US practices may be limited.

My Practice

Currently, we will continue to consider endoscopic therapy in selected patients with pain related to chronic pancreatitis and evidence of PD obstruction amenable to endoscopic intervention (PD stone or stricture in the head, neck or proximal body). To avoid causing duct injury or pancreatitis in healthy pancreas, we may avoid endoscopic intervention if the downstream duct is not affected by chronic pancreatitis changes. For stones >5 mm that are amenable to ERCP with pancreatoscopy, we perform electrohydraulic lithotripsy. If this is not possible, we then consider ESWL followed by ERCP for stone extraction.

Importantly, if the patient does not benefit from endoscopic PD decompression, we may recommend referral for surgical evaluation, as several studies, including RCTs, have suggested that long-term outcomes with respect to pain control may be better after surgical vs endoscopic intervention.[12,13]

For Future Research

Long-term follow-up with larger study populations after ESWL/ERCP vs placebo/sham will be helpful to understand if there are any lasting benefits to PD decompression to treat pain in chronic pancreatitis. In addition, investigating optimal approaches to PD decompression (such as comparing ESWL/ERCP vs ERCP with pancreatoscopy-directed lithotripsy for large PD stones) may further inform clinical practice.

Conflicts of Interest

Dr. Zhou and Dr. Eldika report no financial conflicts of interest.

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