

Tracing the Evidence to Address Painful Chronic Pancreatitis With Surgery

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Chronic pancreatitis is characterized by pancreatic endocrine and exocrine insufficiency, along with persistent, and in some cases, unrelenting pain. While pancreatic insufficiency is effectively managed with pharmacologic intervention, the pain



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associated with this condition is difficult to control and commonly leads to severe consequences for the patient. A search of ClinicalTrials.gov for chronic pancreatitis revealed 152 studies, nearly all of which consist of interventions for pain. The current modalities, including pain medication, pancreatic enzyme replacement, behavioral therapy, endoscopic treatment, and surgery, all have varying degrees of efficacy. Less-invasive modalities include endoscopic retrograde pancreatography (ERP) with stone extraction, ERP with endoscopic lithotripsy and stent placement, and extracorporeal shock wave lithotripsy (ESWL). Surgical interventions include drainage procedures with attachment of the main pancreatic duct to the intestine or resection of the involved pancreas.

In this issue of *JAMA*, Issa and colleagues¹ from the Dutch Pancreatitis Study Group report the results of the ESCAPE trial—a multicenter randomized clinical trial that investigated the effectiveness of best medical management with endoscopic intervention vs surgery first for obstructive painful chronic pancreatitis. The study randomized 88 patients (44 to each group) and found early surgery provided better pain relief (area under the curve for the Izbicki pain score, 37) compared with medical management (Izbicki pain score, 49) during the 18-month study period (difference, -12 points [95% CI, -22 to -2]; $P = .02$), with fewer interventions (median, 1 with early surgery vs 3 with endoscopy first). Patients in the endoscopy group with pancreatic duct stones with a diameter of greater than 7 mm ($n = 22$) were treated with ESWL along with ERP, stone extraction, and stent placement consistent with international guidelines.² Complete or partial pain relief at the end of follow-up was achieved by 58% of patients in the early surgery group vs 39% of patients in the endoscopy-first group ($P = .10$). These results suggest that surgery should be considered earlier in the course of painful chronic pancreatitis. Complication rates, hospital admissions, pancreatic function, and quality of life did not differ between groups.

This trial provides the strongest evidence to date to inform treatment of chronic pancreatitis in patients with a dilated pancreatic duct and stones. Pain from chronic pancreatitis is due, in part, to elevated interstitial pressure resulting in marginal blood perfusion, low oxygen tension, and constant gland inflammation.³ Patients with normal or small-caliber pancreatic ducts are inconsistently treated with endo-

scopic or surgical techniques, but for patients with a dilated pancreatic duct, decompression with stone removal, pancreatic duct stents, or surgery help to correct interstitial pressure, resulting in diminished pain.

The findings of this trial add to another randomized study that concluded surgery was more effective for painful chronic pancreatitis. In 2007, Cahen et al⁴ reported a trial in which 39 patients were randomized to undergo endoscopic treatment ($n = 19$) either with stone lithotripsy ($n = 16$ of the 19) or pancreaticojejunostomy ($n = 20$). At the 24-month follow-up, patients who underwent surgery had lower pain scores and better physical health summary scores. Complete or partial pain relief was attained in 32% of the endoscopically treated patients and in 75% of patients who underwent surgery ($P = .007$), and patients receiving endoscopic treatment required a median of 8 procedures. A 79-month follow-up of this cohort⁵ reported that 68% (13 of 19) of patients in the endoscopic group required additional procedures compared with 5% (1 of 19) of patients in the surgery group ($P = .001$), and surgery was more effective in providing pain relief (80% vs 38%; $P = .04$). In the endoscopic group, 9 patients (47%) ultimately underwent surgery to address the pain. Another randomized trial that included 72 patients found that absence of pain was more frequent in the surgery group (37% [28 of 76 patients]) than in the endoscopic treatment group (14% [9 of 64 patients]) at 5-year follow-up.⁶ In addition, a 2015 Cochrane review found that surgery was associated with higher likelihood of pain relief compared with endoscopic approaches at 2- to 5-year follow-up (risk ratio [RR], 1.62 [95% CI, 1.22 to 2.15]) and long-term follow-up (≥ 5 years: RR, 1.56 [95% CI, 1.18 to 2.05]).⁷

A key consideration of the study by Issa et al¹ relates to the finding that when the pancreatic duct was cleared endoscopically, pain was improved to a similar degree as in the surgery group (Izbicki pain score, 40 vs 37; eTable 13 in Supplement 2). The ability to clear the duct by ERP alone is influenced by the size of the stone(s) (<10 mm), the total stone burden, and pancreatic duct strictures. It is possible that guided selection of patients with smaller-sized and numbers of stones may be appropriate for endoscopic treatment, limiting the number of interventions. It was notable that pain was not resolved in 24 (62%) of the 39 patients in the endoscopy-first group, and almost half of the endoscopy-first group (19 patients) ultimately underwent surgery or were awaiting surgery at the conclusion of the study.

Nearly every patient (95%) in this trial experienced failure of the first step of optimal medical management, which included using pain medication with adjunctive measures

(including pregabalin) and consultation with a pain specialist and dietitian. Although this was not the main finding of the study by Issa et al,¹ the practicalities of this finding for the treating physician are important. Patients with chronic pancreatitis and a dilated pancreatic duct can and should be treated with medications to address pain, but also should be concurrently referred for ductal drainage early in the course of the disease.

To date, 3 randomized clinical trials that included 199 patients and compared modern endoscopic techniques to surgery have each concluded that early surgery provided more substantial and durable pain relief for patients with

chronic pancreatitis. Although a minority of patients with a limited stone burden may benefit from short trial of endoscopic therapy with 1 or 2 sessions, the ability to identify these patients is not entirely reliable. Patients with a dilated duct often undergo multiple endoscopic procedures and have inconsistent improvement despite high-quality evidence, suggesting that most patients should be considered for surgery early in the course of the disease. Given the available data, gastroenterologists and surgeons should work together closely to achieve the best possible outcomes for patients with chronic pancreatitis.

ARTICLE INFORMATION

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REFERENCES

1. Issa Y, Kempeneers MA, Bruno MJ, et al; the Dutch Pancreatitis Study Group. Effect of

early surgery vs endoscopy-first approach on pain in patients with chronic pancreatitis: the ESCAPE randomized clinical trial [published January 21, 2020]. *JAMA*. doi:10.1001/jama.2019.20967

2. Dumonceau JM, Delhaye M, Tringali A, et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) guideline—updated August 2018. *Endoscopy*. 2019;51(2):179-193. doi:10.1055/a-0822-0832

3. Forsmark CE. Management of chronic pancreatitis. *Gastroenterology*. 2013;144(6):1282-1291.e3. doi:10.1053/j.gastro.2013.02.008

4. Cahen DL, Gouma DJ, Nio Y, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. *N Engl J Med*. 2007;356(7):676-684. doi:10.1056/NEJMoa060610

5. Cahen DL, Gouma DJ, Laramée P, et al. Long-term outcomes of endoscopic vs surgical drainage of the pancreatic duct in patients with chronic pancreatitis. *Gastroenterology*. 2011;141(5):1690-1695. doi:10.1053/j.gastro.2011.07.049

6. Dite P, Ruzicka M, Zboril V, Novotný I. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. *Endoscopy*. 2003;35(7):553-558. doi:10.1055/s-2003-40237

7. Ahmed Ali U, Pahlplatz JM, Nealon WH, van Goor H, Gooszen HG, Boermeester MA. Endoscopic or surgical intervention for painful obstructive chronic pancreatitis. *Cochrane Database Syst Rev*. 2015;3(3):CD007884. doi:10.1002/14651858.CD007884.pub3