

Management of chronic pancreatitis: more pain than gain?

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Chronic pancreatitis is an inflammatory disease of the pancreas; the majority of patients develop abdominal pain, malabsorption, and diabetes during the course of the disease. Some patients develop local complications, such as pseudocysts, biliary strictures or gastric outlet obstruction. Abdominal pain is the most dominant, debilitating, and unrelenting symptom (Fig. 1)¹. There is, however, controversy and a lack of clear and uniform definition of chronic pancreatitis. In daily practice and for research purposes, several diagnostic tools are used, such as the Mannheim, Lüneburg, and Büchler tools². Management is complex and should be evaluated by a dedicated multidisciplinary team. Current guidelines³ recommend endoscopic and surgical treatment of pain in patients with obstructive chronic pancreatitis, and to alleviate pain symptoms after medical treatment has failed.

Despite the available evidence for the effectiveness of surgical therapy, there is ongoing debate on the indication, type, and timing of surgical intervention in patients with obstructive chronic pancreatitis. Some long-lasting beliefs seem to persist, without clear evidence to support them. Some argue against invasive treatment in patients with chronic pancreatitis because they believe that the pain relief seen after endoscopic and/or surgical treatment can be explained by a placebo effect in combination with the natural course of the disease (myth of burn-out theory).

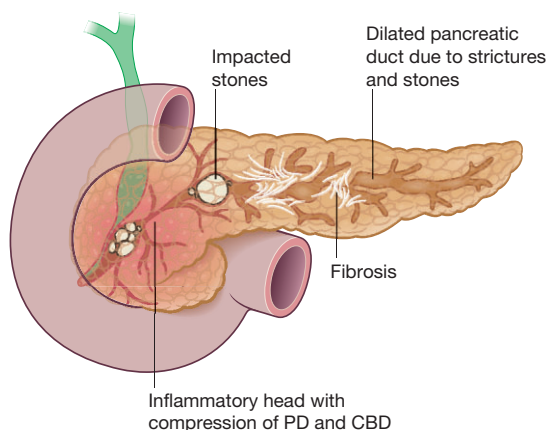


Fig. 1 Pain morphology in chronic pancreatitis

PD, pancreatic duct; CBD, common bile duct.

Such critics refer to studies^{4–6} that have shown a poor correlation between pain symptoms and pancreatic ductal morphology. As such, a sham-controlled RCT (NCT03966781)⁷ is currently evaluating patients with obstructive chronic pancreatitis undergoing either endoscopic retrograde cholangiopancreatography (ERCP) including extracorporeal shock wave lithotripsy (ESWL) or a sham-controlled procedure comprising ERCP without treatment, with follow-up of 6 months. With respect to surgical intervention, a sham laparotomy will be a hard ethical nut to crack. In the burn-out hypothesis, postulated a few decades ago, it is believed that pain relief will eventually come owing to extensive fibrosis as a result of an ongoing inflammatory process in the pancreas. Indeed, fibrosis does occur in all patients, but there is no solid evidence for any relationship with pain relief. On the contrary, studies with more than 10 years of follow-up have shown that a substantial proportion of patients (over 60 per cent) with extensive fibrosis still have severe pain symptoms. Time and again studies have described no relationship between the development of pancreatic function insufficiency due to increasing fibrosis of the pancreatic gland and pain relief. With this in mind, even more convincing evidence against any burn-out theory is the significant and long-lasting pain relief noted after decompression of the pancreatic duct following ESWL, endoscopic, or surgical treatment, despite fibrosis being present^{8–12}. Furthermore, during follow-up in a recent large longitudinal cohort study¹³, about 60 per cent of pain patterns alternated at least once to a different pattern (between continuous, intermittent or no pain).

Medical treatment usually consists of high-dose and multiple opioid analgesics, with serious adverse events, dependency, hyperalgesia, and central sensitization as consequences. There is some evidence that chronic pancreatitis may represent a neuropathic pain syndrome, and can be treated as such with neuropathic pain medication (for example pregabalin), which can be used to avoid the hazardous effect of opioids¹⁴. This is a promising addition to treatments, but the jury is still out as more evidence of its long-term effectiveness is needed. Moreover, it has been shown that prolonged opioid use has a negative influence on the probability of achieving pain relief after surgical therapy, as does the number of endoscopic treatments before surgery¹⁵.

Other pain treatment modalities have been evaluated, such as coeliac plexus block and thoracoscopic splanchnicectomy; these

provide short-term pain relief, but have disappointing long-term effects¹⁶. Endoscopic therapy with ESWL is the surgical counterpart, and provides overall reported pain relief of 32–90 per cent in the long term³. Three RCTs^{8–11} have compared endoscopic therapy with surgical therapy, in which surgical therapy was superior to multimodal endoscopic treatment for persistent pain relief. The first⁸ showed 34 per cent complete pain relief and 52 per cent partial pain relief after surgical management versus 15 and 46 per cent respectively following endoscopic therapy without ESWL in 72 patients after 5 years. In 2007, the CEPAN trial^{9,10} demonstrated that 80 per cent of patients had pain after surgery compared with only 38 per cent after endoscopy at long-term follow-up of more than 6 years among 39 patients randomized to surgery or endoscopy with ESWL. Interestingly, about half of the patients (47 per cent) in the endoscopy group eventually required surgery. The ESCAPE trial¹¹ randomized 88 patients with chronic pancreatitis and a dilated pancreatic duct who had recently been receiving opioids for pain symptoms (less than 2 months strong opioids, less than 6 months weak opioids) to either immediate pancreatic drainage surgery (pancreatojejunostomy or Frey procedure) within 6 weeks after randomization or an endoscopy-first approach according to current stepwise therapy. In the endoscopy-first group, patients received medical therapy (including neuropathic pain medication), if endoscopy plus ESWL failed, and pancreatic drainage surgery if pain symptoms persisted. During 18 months of follow-up, the early surgery group had a lower Izicki pain score (a validated chronic pancreatitis pain score) than patients in the endoscopy-first approach group (37 versus 49), with complete or partial pain relief at the end of follow-up in 58 versus 39 per cent respectively; there were no differences in complications, hospital admissions, pancreatic function, or quality of life. Notably, about half of the patients in the endoscopy-first group underwent or were awaiting surgery after 18 months of follow-up because of persistent pain symptoms.

There is strong evidence that surgery outperforms endoscopic treatment in patients with chronic pancreatitis and a dilated pancreatic duct who have persistent pain symptoms. In the current guidelines³, surgery is still considered a last resort, an escape treatment. These data suggest that surgical treatment should be evaluated early in the treatment process, and not delayed. This means that in selected patient groups (such as those with a dilated pancreatic duct), surgery should be performed immediately after medical treatment has failed, rather than offering repeated endoscopic treatment, usually associated with prolonged opioid use.

Is surgery the holy grail in the treatment of pain in patients with obstructive chronic pancreatitis? Does surgery replace endoscopic treatment? There is evidence that it provides better pain relief than medical and endoscopic therapy, but surgical treatment does not mitigate or prevent pancreatic insufficiency, and patients do not have a better quality of life after surgery than after endoscopic therapy. The complex and invasive nature of the procedure must be kept in mind, especially, for example, in patients with comorbidities and chronic pancreatitis-associated portal/splenic vein thrombosis. Looking closer at the subgroup of patients who underwent ESWL and endoscopic treatment, those with extracorporeal complete duct clearance had pain scores almost as low as those in the surgery group¹¹. In this complex disease, patient-tailored treatment, with careful patient selection for different treatment modalities after multidisciplinary consultation, will lead to the best results using the best of both worlds—endoscopic and surgical. There will be further innovations in endoscopy, with endoscopic laser, electrohydraulic lithotripsy techniques, and intraductal pancreatoscopy

leading to improved duct clearance, and surgery will move towards less invasive approaches, such as laparoscopic or robotic-assisted operations. Treatment should depart from mere stenting and repeated stent exchanges. Complete duct clearance of stones or obstructions is key, either by endoscopy or surgery.

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