

Pain management in chronic pancreatitis: taming the beast

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Abstract: Abdominal pain is a principal and in many cases, the only observable symptom of chronic pancreatitis. Like all chronic pain conditions, managing abdominal pain in chronic pancreatitis remains an onerous task for health care providers. Different mechanisms have been postulated in trying to better understand the pathogenesis of pain in chronic pancreatitis. This review seeks to take a broad look at the various options that are available to providers in trying to achieve pain relief and a better quality of life for chronic pancreatitis patients.

Keywords: chronic pancreatitis, pain management

Introduction

Abdominal pain is a principal and in many cases, the only observable symptom of chronic pancreatitis. It can range from an intermittent, periodical discomfort, especially in the early stages of the disease course, to a more constant debilitating symptom, which is typical of later stages. Pain could occur with or without other symptoms such as nausea, vomiting, and weight loss. Like all chronic pain conditions, managing abdominal pain in chronic pancreatitis remains an onerous task for health care providers. Different mechanisms have been postulated in trying to better understand the pathogenesis of pain in chronic pancreatitis. Pancreatic hyperstimulation, ischemia, and necrosis are some of the more common mechanisms that have been proffered in trying to understand this condition.¹ Oxidative stresses, obstruction of small and large pancreatic ducts leading to ductal hypertension, and necrosis–fibrosis have also been implicated.^{2–4} Most of these theories indicate long-term alcohol abuse as the central cause/starting point of the disease process.⁵ Smoking has also been identified as a cause of chronic pancreatitis. Alcohol exerts toxic effects on the intracellular metabolism of pancreatic acinar cells, resulting in pancreatic lipid accumulation, fatty breakdown, cellular necrosis, and fibrosis. Alcohol is also said to increase the lithogenicity of pancreatic fluid, resulting in stone formation. Long-term contact between stones and pancreatic epithelial cells can lead to scarring as well as cause an increase in pancreatic duct pressure by blockage of ducts as mentioned earlier. The pancreatic duct possesses poor compliance, so the presence of stones easily results in ductal and tissue hypertension leading to necrosis manifesting as severe abdominal pain. The pancreas is an organ that is richly innervated. Inflammation and damage to the pancreatic nerve is also implicated as a cause of pain in chronic pancreatitis. Studies have shown that operations that remove the head of the pancreas in chronic pancreatitis patients have led to significant improvement in pain, as the head of the gland happens to be the most innervated region.^{6,7} It is our belief

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that a better knowledge of the pathogenesis of pain in this condition will lead to better health outcomes.

Pain management modalities

Like most chronic pain conditions, pain management in chronic pancreatitis is best achieved if a graded, multidisciplinary approach is followed. General issues that need to be resolved include making sure that the patient quits alcohol and tobacco use. The expertise of an addiction specialist may be helpful to achieve abstinence from alcohol or smoking. Small meals, low in fat and adequate hydration should be encouraged. Supplementation with medium chain triglycerides (MCT) such as found in the enteral formula, Peptamen® (Nestle HealthCare Nutrition, Inc., Florham Park, NJ, USA), has also been shown to be beneficial. Shea et al conducted a prospective study of eight patients with chronic pancreatitis who were placed on three cans per day of the enteral formulation containing MCT and hydrolyzed peptides for 10 weeks.⁸ Baseline pain scores and cholecystokinin (CCK) levels were determined for 2 weeks prior to the onset of the study. At the end, they concluded that an enteral supplement containing MCT and hydrolyzed peptides minimally increased plasma CCK levels. They also noted an improvement in pain scores from baseline.

Pancreatic enzyme supplementation

Pancreatic enzyme supplements work via a modification of the CCK release feedback mechanism. Typically, the pancreatic enzyme CCK is released from the pancreas for intraduodenal food digestion by CCK releasing factors, which in turn are destroyed by digestive enzyme proteases, creating a negative feedback mechanism.⁹ However in chronic pancreatitis, reduction of intraduodenal free enzyme activity by increased undigested proteins, protease inhibitors, or inadequate pancreatic enzyme secretion allows the CCK releasing factors to survive protease digestion, leading to hyperstimulation of the gland, resulting in a positive feedback mechanism and significant abdominal pain. Pancreatic enzymes are believed to interrupt this positive feedback mechanism and hyperstimulation, resulting in pain relief. Non-enteric and enteric-coated forms of the supplements are available. Presently in the United States, the only Food and Drug Administration (FDA)-approved form is the enteric-coated version. Different studies have been done to verify the efficacy of the supplements with varying results.^{10–13} However, only high doses of the non-enteric versions have been shown to provide pain relief in clinical trials. In cases where non-enteric coated versions are used,

acid suppression with a proton pump inhibitor is highly recommended. Clinical experience has shown some benefit in the administration of pancreatic enzyme supplementation. Some studies have suggested that this benefit may be mostly placebo.^{14,15} Nonetheless, pancreatic enzyme supplementation remains an important pain control modality in chronic pancreatitis.

Analgesics

Analgesics can be non-narcotic or narcotic.¹⁰ Keeping with the graded approach theme, pain management in early stages can respond adequately to non-narcotic analgesia with drugs such as acetaminophen, especially when combined with the early introduction of pancreatic enzymes. However, from clinical experience, abdominal pain quickly becomes more constant and debilitating. Here, introduction of narcotics is considered appropriate. Drugs such as morphine, hydromorphone, and hydrocodone are commonly used in different formulations. These should be introduced while keeping the World Health Organization analgesic ladder in mind.¹⁶ Patients with concomitant renal insufficiency may benefit more from fentanyl. If symptoms are exacerbated to the point of requiring hospitalization, keeping the patient nil by mouth for a short period of time may help reduce pancreatic stimulation and hence pain. Like in every chronic pain condition requiring narcotic medication use, chemical dependency is always a concern and this needs to be carefully and frequently examined by the health care provider, especially in patients who may still have addiction issues with alcohol or smoking. A psychiatric evaluation may be necessary to exhaustively assess chemical dependency. Other medications such as nortriptyline and gabapentin may be necessary in providing neuropathic pain, especially if pancreatic nerve involvement is considered.¹⁷ Use of an acute or chronic pain management service to find the “right” pain regimen for each patient may be necessary. There is no set time or criteria that define when pain management can be upgraded to other more invasive modalities in cases where pain control is not achieved on medications.

Endoscopic ultrasound-guided celiac plexus block

The celiac plexus is a complex network of nerves located in the abdomen where the celiac trunk, superior mesenteric artery, and renal arteries branch from the abdominal aorta. It is behind the stomach and the omental bursa, and in front of the crura of the diaphragm, on the level of the first lumbar vertebra. It is partly formed by the greater and lesser

splanchnic nerves of both sides, and also parts of the right vagus nerve. It consists of the celiac ganglia with a network of interconnecting fibers. A celiac plexus block is commonly used in cases of chronic pancreatitis with pain refractory to conservative pain management measures as described above. The block is usually achieved with steroids in chronic pancreatitis cases although ethanol can also be used. The procedure is commonly done via endoscopic ultrasonography (EUS), but can also be carried out percutaneously and surgically.^{18,19} Some studies have suggested marginal benefit with the percutaneous approach compared to the others.^{19–21} The percutaneous approach has also been suggested to provide better and faster short-term relief.^{20–22} Most of these studies are considered to be small, retrospective studies with a considerable amount of subjectivity. Nonetheless, the EUS guided approach has the advantage of better needle localization of the ganglia and adequate spread of the injectate, resulting in better pain relief and fewer complications. Two main approaches are commonly employed endoscopically: an anterior/anterocrural approach in which there is injection anterior to the diaphragm with diffusion of the injectate over the celiac ganglia, while the classic/retrocrural approach leads to diffusion of the injectate over the splanchnic nerves. A commonly used injectate is the steroid triamcinolone. A minimal amount of alcohol can be added to this for its bactericidal properties. In place of alcohol, broad spectrum antibiotics can also be used. EUS-guided celiac plexus block is a relatively safe procedure. Commonly reported complications, which occur rarely, include: transient diarrhea, asymptomatic hypotension, retroperitoneal abscess, and of course post-procedural pain.²⁴ Eisenberg et al reported that transient diarrhea and hypotension result from the sympathetic blockade that can occur following celiac plexus block and may be seen in up to 38% and 44% of patients, respectively, whether performed by EUS or percutaneous approaches.²⁵ Other complications include lower extremity weakness and paresthesias, paraplegia, pneumothorax, renal puncture, and prolonged gastroparesis.²⁶ As a whole, neurological complications are most related to a posterior approach. Hayakawa et al from Japan reported a case of paraplegia following intraoperative celiac plexus block.²⁷

Endoscopic therapy

As mentioned before, increase in pancreatic duct pressure/ductal hypertension has been postulated as one of the mechanisms of abdominal pain in chronic pancreatitis. This ductal hypertension can result from blockage of the pancreatic duct from any cause such as strictures, stones, or Sphincter

of Oddi dysfunction. The aim of endoscopic therapy is to achieve decompression of the pancreatic duct leading to resolution of ductal hypertension and hopefully pain resolution. Rösch et al conducted a prospective, multicenter study of over 1,000 patients with painful chronic pancreatitis and identified ductal obstruction due to either strictures and/or stones.²⁸ The patients were treated endoscopically at eight different centers and underwent follow-up for between 2–12 years (mean 4.9 years). Of 1,211 patients treated, data was obtained from 1,018 (84%) during follow-up. Of this number, 47% had mainly strictures, 18% mainly stones, and 32% had both strictures and stones. At the end long-term follow-up, 60% of the patients had their endotherapy completed, 16% were still receiving some form of endoscopic treatment, and 24% had undergone surgery. The long-term success of endotherapy was 86% in the entire group, but only 65% in an intention-to-treat analysis. They did not report any significant differences between the patient groups with regard to strictures, stones, or both. Pancreatic function was also not positively affected by endoscopic therapy.

Extracorporeal shock wave lithotripsy (ESWL)

ESWL is employed in the fragmentation of pancreatic duct stones in the hope that the smaller fragments can be easily passed from the pancreatic duct. This is not a commonly used or well-studied modality of pain management. At best, ESWL can be used prior to endoscopic therapy for better outcomes.²⁹

Surgery

This is considered a last option in the treatment of pain in chronic pancreatitis. It is mainly for those who have failed medical or endoscopic therapy. It can also be used to effectively investigate the presence of pancreatic cancer. Surgery follows three options: (1) decompression, (2) resection, and (3) denervation. Obviously, decompression is employed in cases of obstructed pancreatic duct from any cause. Some studies have suggested that surgical forms of decompression may actually be more effective in terms of pain relief in the longer term compared to endoscopic therapy.^{29,30} As stated before, resection of part of the pancreatic gland (head or tail, but not the whole gland) usually leads to pain relief. Resection is considered in patients who have failed other forms of therapy or those who are not candidates for a drainage procedure (usually patients with predominantly small duct disease). This may result in exocrine and endocrine dysfunction, as these patients may not have enough remaining

functioning pancreatic reserve considering their history of chronic pancreatitis.^{6,7,31,32} Denervation can be achieved using an open surgical approach or using thoracoscopic surgery/bilateral thoracoscopic splanchnicectomy.^{33,34} The aim is to interrupt the rich nerve supply from the celiac ganglia and splanchnic nerves. Further study is required into this form of surgical therapy.

Radiation

This is an emerging modality in the treatment of pain in chronic pancreatitis patients. Guarner et al, in a prospective study of 15 consecutive patients who were treated with single dose radiotherapy for painful chronic pancreatitis, found that during follow-up (median: 39 months; range: 4–72 months), 12 patients had no further pain or flare-ups.³⁵ One patient required a second radiation dose 1 year after the initial treatment, but remained well since then (50 months at the time of reporting). Two other patients did not respond to radiotherapy. After radiotherapy, either exocrine or endocrine pancreatic function, or both, deteriorated in three patients. They concluded that radiotherapy for severe symptomatic chronic pancreatitis appears to be a useful and effective therapeutic choice that could potentially substitute for or delay surgery. Further research into this area is needed.

Conclusion

As a whole, chronic pancreatitis is a condition that is not yet fully understood. What remains clear is that therapy for pain needs to be individualized by understanding the possible pathogenesis at play for each patient. After that is achieved, a graded, multidisciplinary approach is most beneficial.

Disclosure

The authors report no conflicts of interest in this work.

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