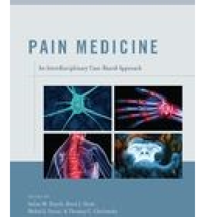

Pain Medicine: An Interdisciplinary Case-Based Approach

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CHAPTER

18. Pain from Chronic Pancreatitis

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Abstract

This chapter presents a clinical case of chronic pancreatitis. Pain from chronic pancreatitis may be caused by localized inflammatory infiltration of sensory nerves, pressure changes in the pancreatic duct secondary to obstruction, direct changes of dorsal root ganglia of neurons innervating the pancreas, visceral hyperalgesia, or central and peripheral sensitization. The chapter discusses how to confirm a diagnosis of pain from chronic pancreatitis as well as its etiology and clinical presentation. Techniques for managing the condition include lifestyle changes; pharmacotherapy; psychological interventions such as biofeedback, hypnosis, and cognitive-behavioral therapy; nerve blocks; ablative and neuromodulation procedures; and surgery. An integrated biopsychosocial treatment combined with comprehensive treatment for chronic abdominal pain may offer better clinical outcomes.

Keywords: abdominal pain, chronic pancreatitis, autoimmune pancreatitis, intraductal stones, pancreatic pseudocysts, strictures of the main pancreatic duct, alcoholism

Subject: Neurology, Anaesthetics, Pain Medicine

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Case Presentation

A 42-year-old woman continues to have abdominal pain 4 years after her last hospitalization for exacerbation of chronic pancreatitis (CP) due to unknown cause. She has constant pain and intermittent exacerbations that can be severe. She is treated with short-acting opioid analgesics by her primary care physician, but the same physician will no longer prescribe more opiates because she has been asking for a dose increase. She is treated with hydrocodone/APAP 10/325 mg PO q6h PRN; her primary care physician suggested an antidepressant, but she is hesitant to use it.

Past medical history is significant for migraine and hypertension.

Past surgical history: tonsillectomy.

On examination, the patient's abdomen is soft and tender in the epigastrium, as well as in the right upper quadrant. No allodynia is noted, but some hyperalgesia is observed. Carnett sign is negative.

Questions

1. How is pain generated in CP?
2. What is the etiology of CP?
3. How is CP clinically presented?
4. How is a diagnosis of CP established?
5. How is the pain from CP managed?
    a. Conservative treatment
    b. Psychological interventions
    c. Nerve blocks and ablative and neuromodulation procedures
    d. Surgical interventions

How Is Pain Generated in CP?

Chronic pancreatitis is a frequently painful disease state, and its pain can be caused by several mechanisms. Localized inflammatory infiltration of sensory nerves can produce a nociceptive type of pain. In human and animal models, the degree of inflammation correlates with the severity of the pain.[1] Pressure changes in the pancreatic duct secondary to obstruction may also cause such nociceptive pain, thus suggesting that decompression procedures may relieve it.[2] A neuropathic pain component can occur in CP and may be relayed through direct changes in the dorsal root ganglia of neurons innervating the pancreas.[3] Patients with CP may develop visceral hyperalgesia that may perpetuate neuropathic pain.[4] Central and peripheral sensitization does develop in animals with CP.[5]

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What Is the Etiology of CP?

Various causes of CP have been identified including autoimmune, hereditary (e.g., cystic fibrosis gene mutation), metabolic, and idiopathic, but the most predominant cause is still alcoholism, in about 51% of patients. Although a hereditary form of CP is clinically seen relatively early in life, alcoholic pancreatitis is mainly present after 40 years of age.[6] Autoimmune pancreatitis may be an IgG4-related disease with onset after the age of 50; it occurs mainly in men. Obstruction of the main pancreatic ducts may be caused by scarring, tumors, intraductal stones, or stenosis of the papilla of Vater. Obstructive CP can be caused by narrowing or stricture of the main pancreatic duct. A large subset of patients requiring surgery have no discernible cause and are considered to have idiopathic pancreatitis.

How Is CP Clinically Presented?

Abdominal pain is the most predominant symptom, one that can influence quality of life, reduce food intake, and result in an excessive use and misuse of narcotic analgesics. Many patients complain of epigastric pain that may radiate to the back, may increase after fatty food ingestion, and is described as boring, deep, sharp, and penetrating. It is often associated with nausea and vomiting.

p. 290 When pancreatic lipase secretion is significantly reduced, steatorrhea will occur. This is a symptom of advanced CP in which most of the acinar cells have been destroyed, but significant weight loss due to maldigestion is uncommon. Endocrine insufficiency may result in diabetes mellitus in up to 80% of the patients with CP. Other symptoms include jaundice, painful joints, abdominal distension, shortness of breath and pleural effusions, and pancreatic ascites.

How Is a Diagnosis of CP Established?

Physical examination does not give much additional information except for abdominal tenderness and possibly jaundice from distal biliary obstruction. In contrast to acute pancreatitis, serum lipases and amylase are normal in CP. Complete blood count, electrolytes, and liver function tests are often normal. Elevated serum bilirubin and alkaline phosphates can be indicative of intrapancreatic bile duct compromise.

It seems that functional pancreatic activity assessment (secretin and cholecystokinin [CCK]) is unnecessary in advanced chronic disease because imaging tests typically reveal morphologic changes, and these images can also be used as a guide to enzyme therapy. Quantifying enzymes (tryptase, amylase, lipase) and bicarbonate levels helps in assessing the residual functional mass of pancreas. A low level of trypsinogen has a high specificity for CP.

Five pancreatitis susceptibility genes are established: cystic fibrosis transmembrane conductance regular gene (CFTR), pancreas secretory trypsin inhibitor gene (SPINK-1), chymotrypsinogen Cgene (CTRC), calcium sensing receptor gene (CASR), and cationic trypsinogen gene (PRSS); these are linked to hereditary pancreatitis. However, routine full genetic analysis is not recommended in CP; these tests are expensive and do not contribute to establishing a diagnosis.

Diffuse calcifications on plain X-ray or computed tomography (CT) are pathognomonic for CP, but they frequently occur late in the disease course. Better specificity can be obtained by endoscopic ultrasound, which can show parenchymal changes (atrophic and fibrosis) and ductal features suggestive of CP. A reproducible set of endoscopic ultrasound criteria, the Rosemont criteria, help categorize the often subtle morphologic changes in the gland. CT with contrast provides more details about pancreatic inflammatory mass, calcifications, and

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duct dilation and can additionally identify pseudocysts, splenic artery pseudoaneurysms, and biliary duct involvement.[7] Unlike CT, magnetic resonance imaging (MRI) presents no radiation risk, and it can detail calcifications, atrophy, ductal abnormalities, fluid-filled cysts, and neoplastic masses. MRI better defines the biliary and pancreatic ductal anatomy and is currently preferred for surgical planning in lieu of endoscopic retrograde cholangiopancreatography (ERCP).

ERCP is used in complicated acute and chronic pancreatitis, principally for therapeutic interventions. A differential retrograde epidural block is a diagnostic test used for initial evaluation of the neural mechanisms in chronic abdominal pain. In patients with visceral pain, a differential retrograde epidural block is used as a diagnostic modality to identify which patients should receive celiac, splanchnic, or hypogastric blocks. The specificity, sensitivity, and predictive value of this test still need to be established.[8,9]

How Is the Pain from CP Managed?

Conservative Treatment

The management of CP is mainly directed at the treatment of persistent pain. Some lifestyle changes are necessary, such as abstinence from alcohol even in those forms of pancreatitis that are not linked to alcohol consumption. Smoking cessation is essential. These lifestyle adjustments may reduce pain and improve life expectancy.[10,11]

Pharmacological management of chronic pain from CP may be complicated by liver and renal insufficiency, and the medication schedule needs to be adjusted accordingly.

Acetaminophen can be used for mild pain, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) can be justified despite their potential side effects that may include dyspepsia, gastric ulcerations, and even renal toxicity. Short-acting opioid preparations are suitable for more severe breakthrough pain, whereas long-acting preparations are used for more severe constant pain with or without breakthroughs. It may be necessary to combine both in some patients with persistent severe pain with breakthroughs. Their common side effects, such as nausea and vomiting, can be managed with low doses of a centrally acting antiemetic, whereas constipation can be managed with laxatives. Opioids bind to opioid receptors (μ, κ, and δ) that are invariably found in the sphincter of Oddi. Opioids may result in an increase in the contraction frequency, amplitude, and tonic rest pressure of the sphincter of Oddi muscular valve. Because this effect can only partly be counteracted by naloxone (an opioid antagonist), it is likely that the effect of morphine, or possibly other opioids, on the sphincter of Oddi is mediated by several opioid receptors. It is not clear if such increased sphincter pressure may indirectly cause development or deterioration of acute or CP.[12,13,14]

Membrane stabilizers and antidepressants for chronic pain are used predominantly for neuropathic pain but can be used for the treatment of CP. Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) are frequently prescribed. Calcium channel blockers like pregabalin or gabapentin are effective in treatment of chronic pain from CP and may provide an opioid-sparing effect.[15,16]

Ketamine in various doses has been used for treatment of chronic pain. An S-ketamine infusion for chronic pain from CP reduces hyperalgesia immediately after such infusion.[17]

Pancreatic enzyme supplementation may help in controlling chronic pain by, in optimal dosing, degrading CCK-releasing factor and thus lowering the CCK levels. The best results of therapeutic pancreatic enzyme supplementation were achieved in small duct disease or minimal-change p. 291 ↳ CP.[18] Octreotide, an inhibitor of

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the exocrine secretion of the pancreas, may provide analgesia by anti-inflammatory action, reduction of sphincter of Oddi pressure, and inhibition of neural stimulation.[18]

Various endoscopic and percutaneous interventions may provide pain relief in patients with CP. If the pancreatitis is caused by intraductal stones, extracorporal shock wave lithotripsy combined with endoscopic extraction of the stones has a relatively high success rate.[19] If the pancreatitis is caused by strictures of the main duct, stenting with endoscopic drainage seems to be the therapy of choice.[20] Pancreatic sphincterotomy should be performed prior to any stricture treatment.[21,22] Pancreatic pseudocysts can be also drained endoscopically; this approach has lower costs but may provide a therapeutic effect similar to that achieved by surgery.

Psychological Interventions

Psychological treatments can improve chronic abdominal pain, and such treatment should be considered in most patients with persistent pain from CP. Those who have moderate or severe symptoms or whose pain is potentiated by stress or emotional symptoms should be provided with such a comprehensive approach.[23,24] It is the opinion of this group of physicians that such therapy should be initiated in parallel with other listed therapeutic approaches presented here and, if appropriate, continued throughout the course of treatment.

Biofeedback is one of the therapeutic approaches used to allow a patient to regain control of his or her physiological systems' functioning through the use of various mechanisms that demonstrate changes in the activity of those same systems brought about by the patient's activity. Studies on biofeedback have been promising, but current clinical evidence is rather insufficient to support its use in some painful abdominal states.[25] Previously, at least one study using thermal biofeedback suggested benefits for treatment of recurrent abdominal pain,[26] and electromyelographic (EMG) biofeedback may be beneficial in reducing constipation.[27,28] Relaxation training involving progressive muscle relaxation, thermal biofeedback, cognitive therapy, and education implemented through biofeedback training may provide some relief from chronic abdominal pain, particularly in irritable bowel syndrome (IBS).[29,30]

Hypnosis has been utilized in the treatment of various chronic pains, despite a lack of knowledge on how analgesic hypnosis actually works. In general, induction of relaxed states of focused attention and inner absorption, with a relative suspension of peripheral awareness, is combined with suggestions for pain control.[31] The primary focus of hypnotherapy research, when it comes to abdominal pain, is on IBS, with three randomized studies providing evidence for a reduction of IBS symptoms and improvement in quality of life.[32] Hypnotherapy also improved visceral pain thresholds, which could suggest similar effects in other chronic abdominal pain states.[33]

Cognitive-behavioral therapy (CBT) is psychotherapeutic approach focusing on those thoughts and feelings that influence a patient's behaviors. CBT implements various behavioral (e.g., relaxation, coping skills training) and cognitive approaches to reduce pain and pain-related disability.[34] CBT was mainly studied for pain control in IBS, with mixed results.[35,36]

A multidisciplinary chronic pain rehabilitation program that includes patient education, physical therapy, occupational therapy, medication management, individual psychotherapy, group therapy, cognitive therapy, thermal biofeedback, weaning of opioids and habituating substances, substance use education, and progressive muscle relaxation may provide both short- and long-term benefits in improving chronic pain.[37,38]

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Nerve Blocks and Ablative and Neuromodulation Procedures

Nerve blocks, ablative procedures, and neuromodulating techniques aim at interrupting or modulating neural/pain conduction; when used for abdominal pain relief, multiple mechanisms of action have been speculated.

Historically, splanchnic nerves, mainly greater and lesser, and the celiac plexus were considered likely targets for pain control. In general, sympathetic innervation of the abdominal organs consists of preganglionic fibers of T5–T12 that merge with the ventral rami. Together with communicating rami, they course in the direction of the sympathetic chain. They synapse at the level of the celiac, aortorenal, and superior mesenteric ganglion.

Splanchnic nerves confluence with the vagal preganglionic parasympathetic fibers, sensory fibers of the phrenic nerve, and postganglionic sympathetic fibers to form the celiac plexus, which is widely spread around the abdominal aorta, especially anteriorly. The location of the splanchnic nerves is in a narrow space between the lateral border of the vertebra and medial pleura.[39]

Although commonly used nerve blocks using long-acting local anesthetic may significantly reduce the pain caused by pancreatic cancer and pancreatitis, neurolysis of the celiac plexus using alcohol or phenol provides prolonged pain relief in those patients with end-stage pancreatic cancer.[40] Limited use of such neurolytic agents in cancer patients is advised due to the unpredictable flow of the agent and therefore uncontrolled lesion size; this can result in rare catastrophic consequences like paraplegia and retroperitoneal fibrosis.

Splanchnic and celiac plexus blocks are performed percutaneously under fluoroscopic guidance. Several approaches, such as transaortic, retrocrural, and transdiscal, are used without a clear advantage accruing to the use one over another[41] (Figure 18.1).

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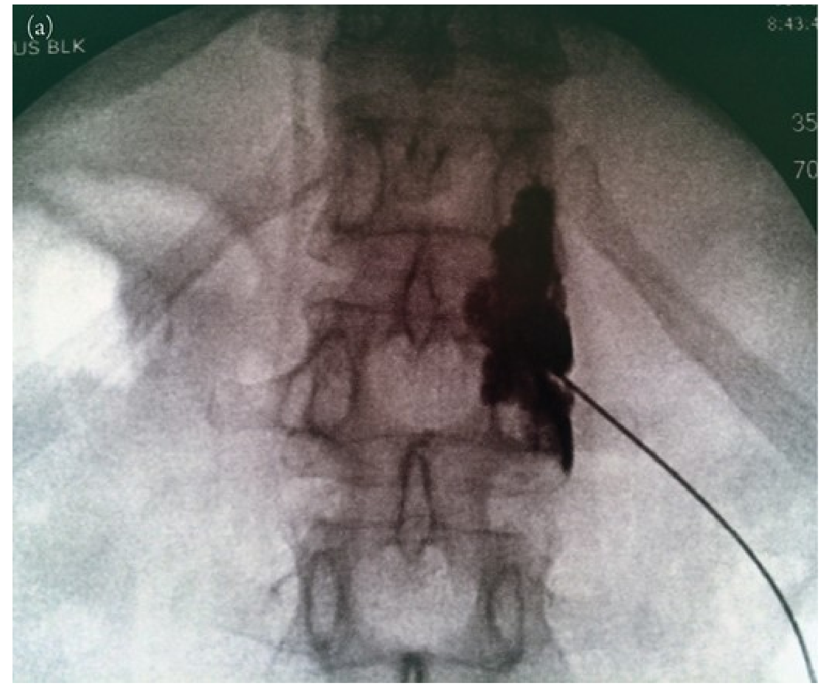

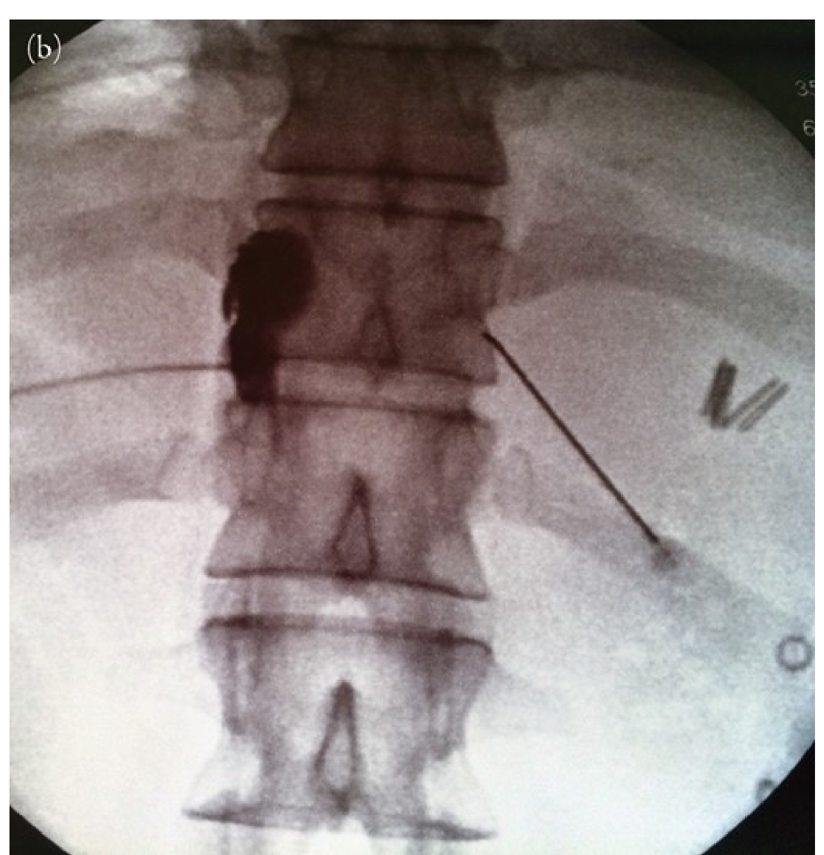

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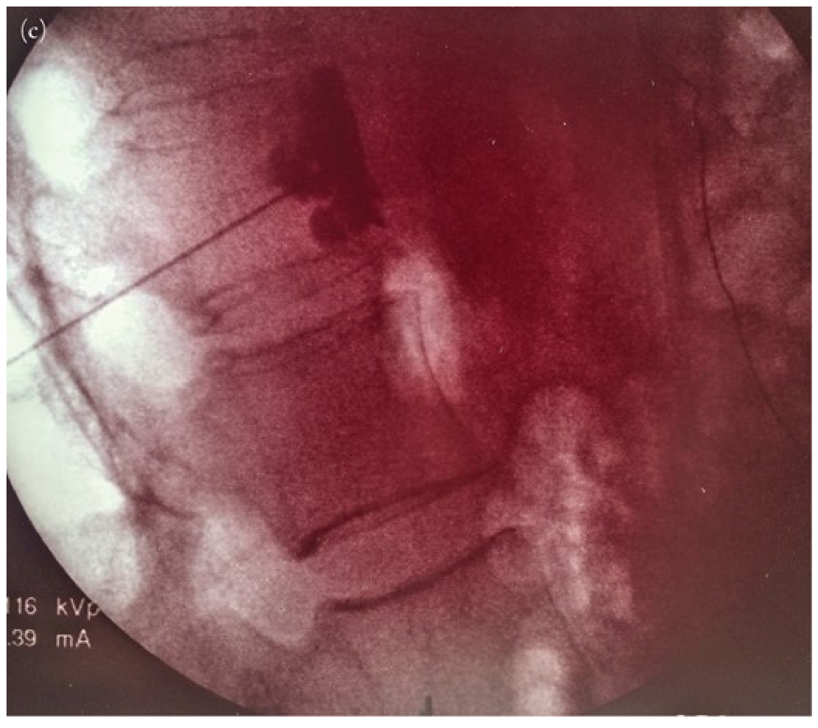

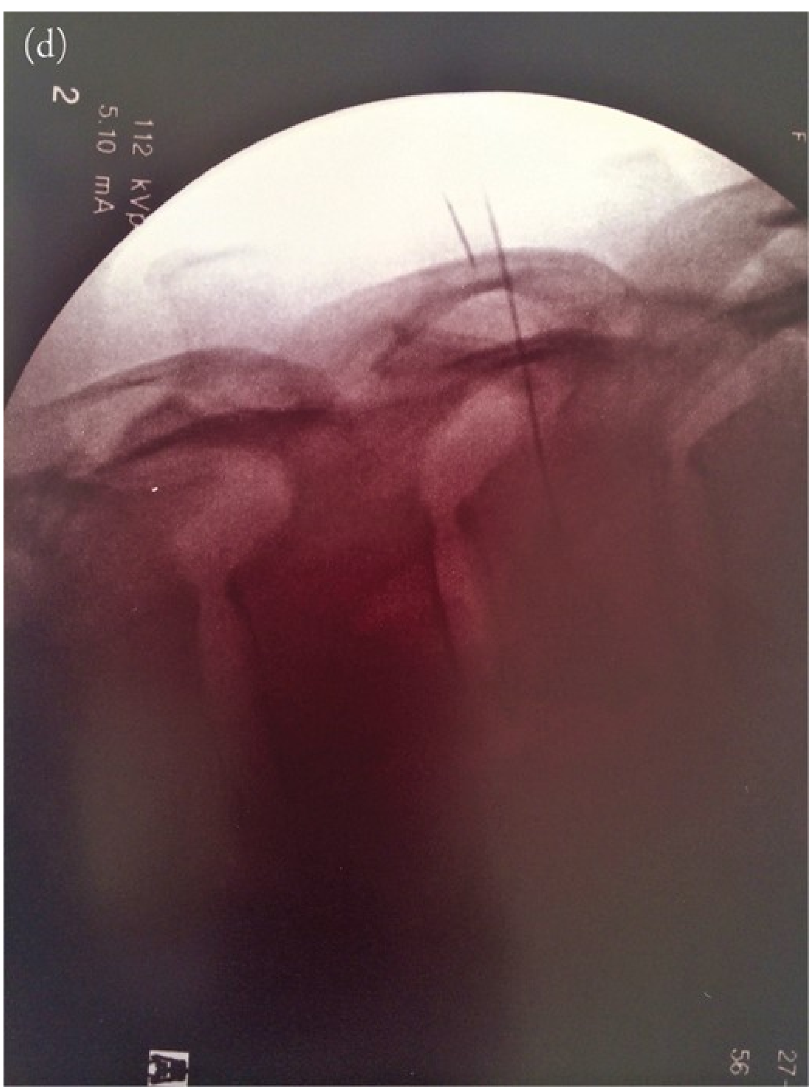

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Figure 18.1 Celiac plexus (A) and splanchnic nerve block (B) needle and contrast position in AP intraprocedural fluoroscopic view. Approximately 20 cc of 0.375% bupivacaine was injected bilaterally during celiac plexus block (A) and 10 cc bilaterally during splanchnic nerve block (B) following contrast dye verification of proper needle placement. Notice that the needle at the T11 level (B) when used for the splanchnic block is kept in contact with the concavity of the T11 vertebral body and in the posterior third of the body width. Needle passage to the vertebral body is always maintained at the top of the corresponding foramina in order to minimize the frequency of possible paresthesias.

Although computed tomography (CT) guidance provides better visualization of the anatomic structures during more demanding neurolytic celiac plexus block, in patients with nonmalignant pain, repeated exposure to radiation and the expense of CT guidance does not justify its use.[42]

Endoscopic ultrasound guidance for celiac plexus block or celiac plexus neurolysis provides good pain relief in only 55% of patients at 4 and 8 weeks follow-up. Complications from the endoscopic approach are at about 1.8%, and these include the possibility of major complications such as paraplegia.[44]

Splanchnic nerve blocks are frequently followed by radiofrequency (RF) denervation for prolonged pain relief (Figure 18.2). Predictable nerve position and a low frequency of serious complications compared to neurolytics are advantages of splanchnic RF.

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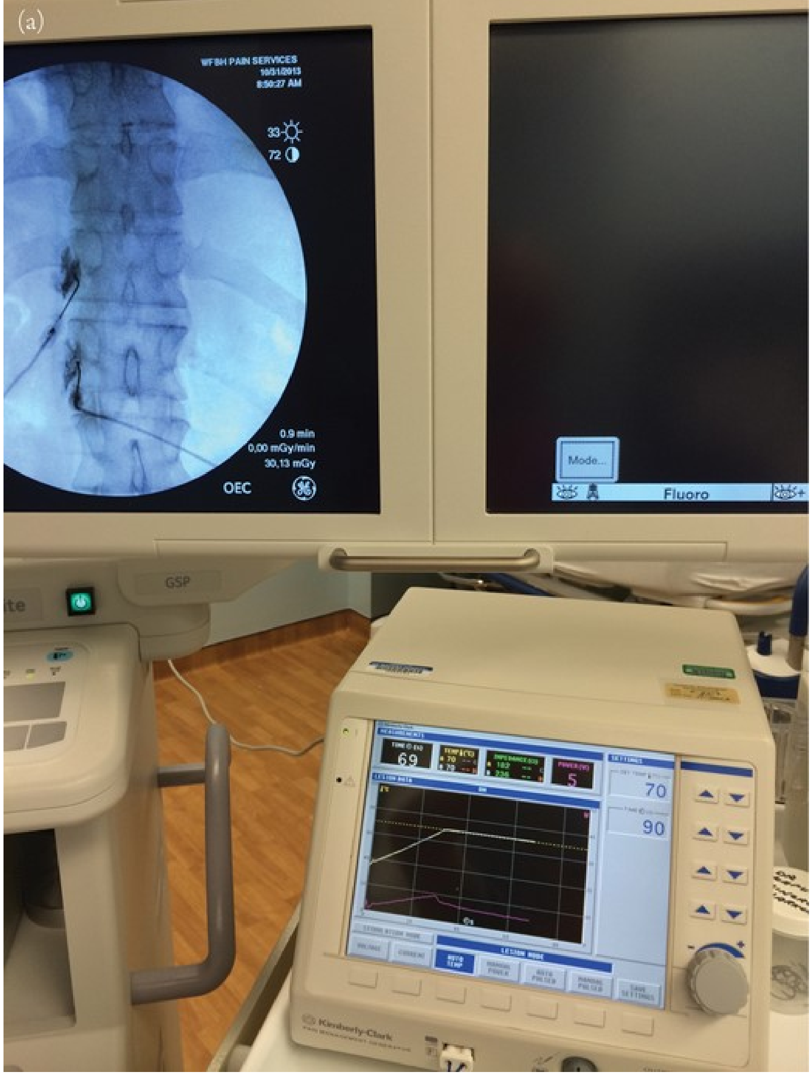

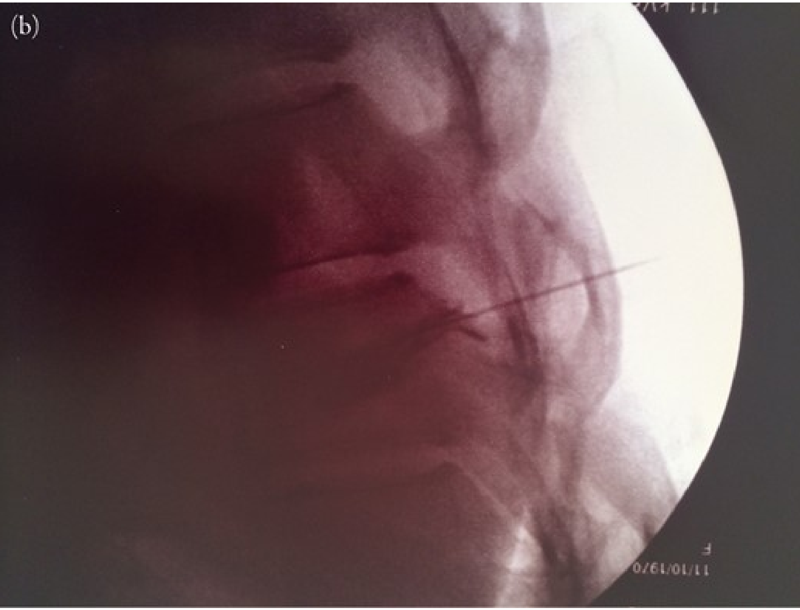

Figure 18.2 Radiofrequency (RF) denervation of splanchnic nerves. A. The RF setup during splanchnic denervation showing in the upper left corner a proper AP fluoroscopic view of the electrodes. In this case 20-gauge, 100 mm, 10 mm active tip curved RF needles were positioned on the left side of vertebral body of T11 and T12.

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Contrast should be used before lesioning to ensure extravascular and extrapleural position of the RF needles. The RF generator is adjusted to 70°C, and lesioning time is 90 seconds.

Two larger case series on the use of RF ablative procedures suggested a significant improvements in pain scores for patients who suffer from CP[45,46]; 73 out of 107 patients who positively responded to a diagnostic block were followed prospectively. Whereas 38 of them received another block, 31 received RF treatment. In both groups, pain relief of greater than 50% was found in 40% of patients. Another study[46] described the long-term effects of splanchnic RF in 10 patients with a follow-up of about 18 months. A significant reduction of pain scores, use of opiates, and frequency of acute hospitalization was reported.

Better pain control was also reported over a mean period of 45 weeks in 11 out of 18 patients, and opioid use was significantly reduced.[47] Patients with previous positive responses had repeated denervation with repetitive comparable therapeutic effect. Return of abdominal pain was speculated to be caused by nerve regeneration. Complications may include postprocedural neuritis and, more frequently, hypotension and diarrhea.

 Despite the fact that thoracoscopic splanchnicectomy for pancreatic pain is, at least initially, a highly successful procedure in alleviating pain from CP, patients' chronic pain returns at 6 months in about 25% of those treated and in more than 50% of patients in the long-term. Splanchnicectomy is an extensive procedure involving dissection of the parietal pleura and transection of the splanchnic nerve fibers at the thoracic level, and the risks of anesthesia with an endotracheal double-lumen tube in the prone position cannot be discounted. Interestingly, it appears that additional vagotomy does not provide additional pain relief.[48,49]

The use of spinal cord stimulation (SCS) to treat visceral pain and pain from CP was initially presented via several case reports.[50,51] More recently, several larger retrospective publications provided further evidence that SCS may be an effective long-term solution for those patients with severe CP. Two of these studies included patients with clearly identified but various causes of chronic abdominal pain and visceral hyperalgesia,[52,53] whereas a third study included 54 patients with only CP (Figure 18.3). The first study involved 30 out of 35 patients who reported 50% or greater relief of pain at the end of the SCS trial.[52] They were followed for more than 1 year, and they maintained similar pain relief.

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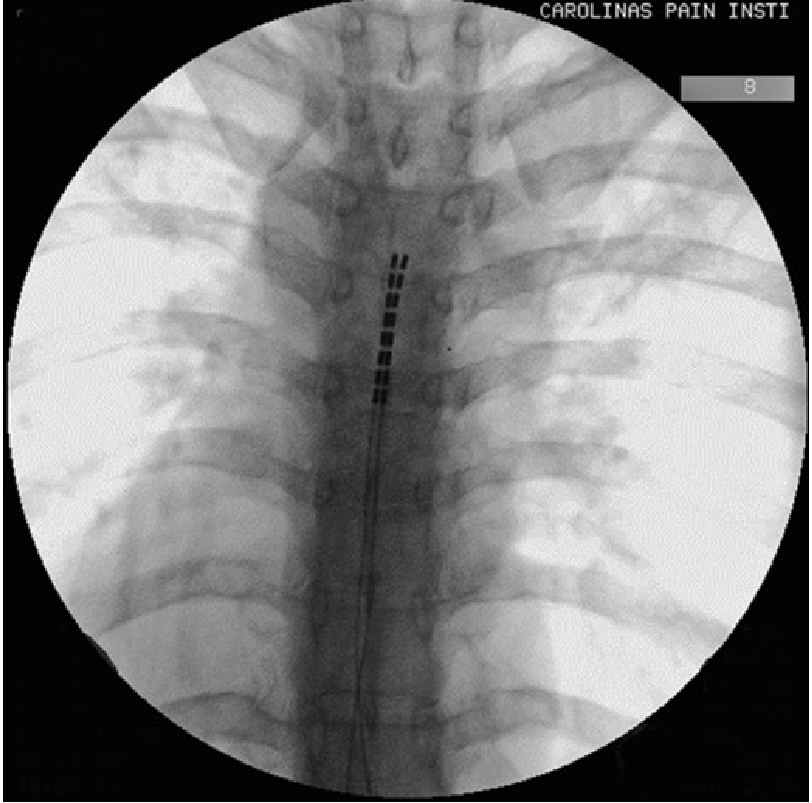

Figure 18.3 Anteroposterior view of the epidural leads using intraoperative fluoroscopy during positioning of two octrode leads. The most common “sweet spot” to achieve proper stimulation within the abdominal area is the midline positioned lead near the top of the T5 vertebral body. Such posterior epidural position was also confirmed in the lateral view.

A comprehensive national survey on SCS for chronic abdominal pain that followed this retrospective study included 76 case reports, and its results were consistent in the technical aspects of SCS implantation, as well as in the opioid use and pain score improvements.[53] Both studies suggested that the “sweet spot” for SCS when it comes to various causes of chronic abdominal pain is a standard octrapolar lead tip placed near the top of the fifth thoracic vertebral body in the posterior epidural space. Pain relief exceeded 50% in most of the patients, and their long-term opioid use decreased by more than two-thirds.[52,53] In both studies, the largest numbers of participants were patients with severe CP:[52,53] 26 out of 35 patients in the retrospective study and 26 out of 70 p. 294 patients in ↳ the survey study carried a diagnosis of CP. Data from the subgroup of the patients with CP showed similar improvements in pain and opiate use to those in patients with other sources of chronic abdominal pain.

Subsequent retrospective analysis examined 30 consecutive patients with severe pain due to CP who underwent a trial with SCS for 7–14 days. Twenty-four patients reported 80% pain relief at the end of the trial period. After definite implantation, one patient was lost to follow-up, and in three patients the system had to be removed because of infection. At 1-year follow-up, visual analog (VAS) pain scores and opioid consumption were both profoundly reduced, reflecting the results of previous studies.[54] The main complications of SCS are wound infection and lead migration.

An attempt was also made to directly stimulate splanchnic nerves, and this resulted in long-term pain reduction and decreased opioid consumption in one case report of a patient with CP. Octapolar leads were placed along the mid-vertebral body of T11–T12 and connected to an implantable pulse generator using a relatively simple approach with stable lead placement. This therapy should be investigated further.[55]

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Surgical Interventions

Surgery for pain relief in CP should be considered if medical or endoscopic treatments do not provide satisfactory pain relief. Chronic pain from CP can be improved by using a variety of surgical procedures tailored to the specific morphology of the disease. The two general surgical procedures are duct decompression with or without resection. The goal of surgical treatment is to alleviate all manifestations of the disease while minimizing parenchymal loss.[56,57]

A lateral pancreaticojejunostomy, the Partington-Rochelle modification of the Puestow procedure, is a proven procedure that purely achieves ductal drainage. This spleen-preserving longitudinal drainage procedure can be accomplished with low morbidity and mortality rates. This procedure has been one of the dominant pancreatic procedures; short-term pain relief is achieved in more than 75% of patients, but this success rate falls off over time to roughly 50% at 5–7 years of follow-up. Other procedures that are principally used for ductal drainage include any of the sphincter-directed therapies, such as minor sphincteroplasty for pancreatic divisum or dual (biliary and main pancreatic duct) sphincteroplasty for sphincter of Oddi dysfunction. These procedures for ductal drainage have the highest degree of parenchymal sparing.

Some extent of resection is a component of all other forms of surgical treatment for CP. The procedures most commonly considered to be extensions of ductal drainage are the Frey and DuVal procedures. The Frey procedure includes incomplete resection of the pancreatic head in conjunction with the later longitudinal drainage of the duct, as is done in a Puestow procedure. The procedure has generally superseded the Puestow procedure in most patients requiring ductal drainage, especially if there is an inflammatory head mass. The Frey procedure has been shown to have superior results compared to other pancreatic head resections in randomized trials. The DuVal procedure includes a short distal pancreatectomy with drainage of the duct into a Roux jejunal limb for ductal decompression. More extensive resections occur in distal or subtotal pancreatectomy, Whipple, Beger, and Berne procedures. Distal pancreatectomy of any amount that does not include ductal drainage should be reserved for patients with clearly focal disease in the body and tail of the pancreas.[57] The Whipple procedure is performed similarly to the operation done for pancreatic cancer, and, in fact, the concern for pancreatic cancer in a patient with CP would be a reason to select this procedure. The operation includes cholecystectomy and excision of the distal bile duct, duodenum, and head of the pancreas. It is particularly useful in patients with multiple complications of CP, including biliary or duodenal obstruction, particularly with a head mass. In the United States, it is the most common resection done for CP involving the pancreatic head. The Berger procedure is a duodenum-preserving resection of the pancreatic head that includes subtotal resection of the pancreatic head, transection of the neck of the pancreas, and drainage by pancreaticojejunostomy. The Berne procedure includes an isolated head resection, similar to the Beger, but without division of the pancreatic neck. Both Beger and Berne procedures have the advantage of not including resection of the duodenum, which may contribute to the favorable results shown in clinical trials when compared to the Whipple procedure. All of these head resections are more complex procedures with higher morbidity than other pancreatic procedures, but, for properly selected patients, they show good early pain relief profiles. Total pancreatectomy is considered the most drastic form of resection and is indicated in some patients with CP. It is considered for patients with disabling quality of life from CP that is due to genetic abnormalities or idiopathic CP. The metabolic consequences of total pancreatectomy are significant, but the procedure treats completely the organ involved. To mitigate the metabolic endocrine consequences of the operation, specialized centers have included the addition of islet autotransplantation. This allows partial or complete independence from exogenous insulin by native islets that are liberated from the gland and infused into the liver via the portal vein. Complete insulin independence occurs in approximately in 25–35% of patients, but the remainder of patients are usually pleased with the small amounts of insulin they require for glucose control. The operation is effective in pain control and improvement in quality of life in properly selected patients.[57]

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Recent studies suggest that preoperative opioid use is a negative predictor of long-term pain relief after either surgical or endoscopic interventions. It could be that central sensitization or opioid dependency may be causes.[58,59] Earlier surgical interventions likely provide better pain relief compared to endoscopic interventions, and they carry similar complication rates.[60,61]

Conclusion

When establishing a pharmacological treatment plan for chronic abdominal pain, nonanalgesic drugs should also be p. 295 ↳ considered. Membrane stabilizers and antidepressants for pain, such as calcium channel blocking agents or norepinephrine reuptake inhibitors, seem to be effective. Other potential targets in the treatment of chronic abdominal pain are nerve growth factor inhibitors and the TRPV1 antagonist. Concerning central sensitization, indirect N-methyl-D-aspartate (NMDA) receptor antagonists may be found useful in the future despite their very narrow therapeutic window.

Chronic abdominal pain is a complex physical and psychological problem that requires an understanding of its clinical, physical, and psychosocial features and providing treatment options tailored to the needs of patients. An integrated biopsychosocial treatment plan combined with comprehensive treatment for chronic abdominal pain may offer better clinical outcomes.

Despite the fact that celiac and splanchnic nerve blocks were long a part of the armamentarium of pain physicians, RF denervation of the greater and lesser splanchnic nerves to provide prolonged treatment effects needs to be studied in a formal, randomized, prospective study. SCS appears to be a robust yet minimally invasive therapy that has a promising future when it comes to pain control from CP. Comparative studies between surgery and endoscopic treatment show evidence in favor of early surgery.

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