Pancreatic cancer and chronic pancreatitis commonly produce pain that is difficult to control.\(^1,2\) Initial therapy with nonsteroidal anti-inflammatory agents (NSAIDs) is often inadequate and necessitates opioid administration. Although opioids effectively relieve pain, they are associated with dry mouth, constipation, nausea, vomiting, drowsiness, delirium, and may impair immune function.\(^3,4\) In addition, patients with chronic pancreatitis risk narcotic dependence. Therefore, nonpharmacologic therapies, such as celiac plexus neurolysis (CPN), are often given with the goal of improving pain control and quality of life while reducing the risk of drug-related side effects.

Some use the term celiac plexus block (CPB) to refer to the use of steroids and/or a local anesthetic to temporarily inhibit celiac plexus function in patients with benign disease (chronic pancreatitis). The term celiac plexus neurolysis is often applied to techniques that inject alcohol or phenol to induce neurolysis in patients with pancreatic cancer and other malignancies. Many use these terms interchangeably.

This review summarizes the percutaneous (PQ) and surgical methods of CPN and focuses on the technical aspects of EUS-guided CPN (EUS CPN). Publications specific to EUS CPN are reviewed, and evidence-based guidelines regarding the indications and role of EUS CPN are developed. Potential future areas of investigation are raised where evidence is incomplete.

### CURRENT TECHNOLOGY

Although the terms “celiac plexus” and “splanchnic nerves” often are used interchangeably, they are anatomically distinct structures (Fig. 1).\(^6-8\) The splanchnic nerves are located cephalic to the diaphragm (retrocrural) and typically are anterior to the twelfth thoracic vertebra. The celiac plexus is located caudal to the diaphragm (antecrural), surrounds the origin of the celiac trunk, and is composed of a dense network of ganglia and interconnecting fibers. Ganglia vary in number (1-5), size (diameter 0.5-4.5 cm), and location (T12-L2).\(^6\) The celiac plexus transmits the sensation of pain for the pancreas and most of the abdominal viscera except for the left colon, rectum, and pelvic organs.\(^9-11\) Stimuli reach the thalamus and cortex of the brain, and this information is perceived as pain. Descending inhibitory mechanisms may also modulate the ascending pain information.

Kappis\(^12\) described the classic technique of CPN in 1914 (Fig. 2). Modifications have been created in an attempt to improve the accuracy of needle placement and pain relief while reducing procedure-related complications. These techniques differ with respect to the route of needle insertion (Figs. 3 and 4), use of radiologic guidance versus a blind procedure, and chemical composition of the injected agent.

For CPN in patients with cancer, the injected agent usually includes a local anesthetic (bupivacaine or lidocaine) and a neurolytic (phenol or alcohol). The...
local anesthetic reduces the discomfort caused by the neurolytic. Phenol produces minimal pain because of its local anesthetic effect. Although direct comparisons between alcohol and phenol have not been performed, alcohol is favored because it induces greater neurolysis and presumably greater pain relief. For CPB in patients with chronic pancreatitis, most physicians inject a steroid in place of the neurolytic agent.

Three meta-analyses have reached conflicting conclusions regarding PQ CPN for intra-abdominal malignancy. Lebovits and Lefkowitz concluded that CPN leads to successful relief of pancreatic cancer pain. Sharfman and Walsh found their data insufficient to judge the efficacy, long-term morbidity, or cost effectiveness. Most recently, Eisenberg et al. reviewed publications from 1966 to 1993, including 24 studies, of which 2 were randomized controlled trials, 1 was prospective, and 21 were retrospective uncontrolled trials. The cancer type was specified in 1117 patients (63% pancreatic, 37% non-pancreatic). Good to excellent pain relief was reported in 89% of patients during the first 2 weeks after CPN. Partial to complete pain relief was reported in about 90% of patients at 3 months and 70% to 90% at the time of death. Interestingly, pain relief was not influenced by the technical approach or the use of radiologic guidance. The most common side effects were local pain (96%), diarrhea (44%), and hypotension (38%), and these were generally mild and transient. The investigators concluded the following: (1) CPN has long-lasting benefit for 70% to 90% of patients with pancreatic and other intra-abdominal cancers, regardless of the technique used, and (2) adverse effects are common but generally transient and mild.

More recently, a prospective, randomized, double-blind study of 24 patients with pancreatic cancer who underwent PQ CPN was reported. The CPN group had a statistically significant reduction in analgesic consumption and drug-induced side effects versus patients treated with drugs alone. In a different study, Kawamata et al. showed that CPN results in less deterioration in quality of life for pancreatic cancer patients when added to morphine therapy compared with morphine therapy alone or NSAIDs alone, because of the increased duration of the analgesic effect and reduced opioid side effects.

Major complications develop in about 1% to 2% of patients and include lower extremity weakness and paresthesia, paraplegia, puncture of adjacent organs, and chronic gastroparesis and diarrhea. Neuro-
logic complications result from spinal cord ischemia or direct injury to the spinal cord or somatic nerves. Spinal cord ischemia may result from thrombosis or spasm of the artery of Adamkiewicz located on the left of the spine between T8 and L4, which perfuses the lower two thirds of the spinal cord. Despite theoretical advantages of the given methods, it is believed that the risk of neural dysfunction is not influenced by the technical approach. Paraplegia has been reported with each PQ method regardless of the use of radiologic guidance. There are even several reports of paraplegia after the most direct approach (surgical neurolysis).

Celiac plexus neurolysis may also be performed surgically. Lillemoe et al. published a prospective randomized trial in 137 patients with unresectable pancreas adenocarcinoma. Neurolysis versus placebo improved pain control at 2, 4, and 6 months follow-up. Patients with preoperative pain had a significant survival advantage compared with controls. The reason is unclear but may relate to reduced opioid-induced side effects, improved nutritional status, and emotional well being. To date, no study has reproduced these results. Potential disadvantages of surgical neurolysis include reduced pain relief reported by some, uncertainty regarding response to therapy because of difficulty differentiating postoperative pain from cancer pain, and limited surgical access that may prolong operative time.

Most studies evaluating PQ CPB for controlling pain from chronic pancreatitis have been small poorly designed retrospective case series and have reported disappointing results. Lee et al. found PQ CPN effectively relieves pain associated with malignant disease but is not as effective for benign disease (73% vs. 37% response). Although limited data suggest PQ CPN produces short-term pain relief (weeks to months), extended pain relief typically requires repeat therapy.

TECHNIQUE FOR PERFORMING EUS CPN/CPB

More recently, EUS CPN has been developed for the purpose of enhancing needle localization and spread of the injectate. By doing so, one hopes to minimize complications and improve pain relief. Patients are questioned regarding allergies and use of anticoagulants. Informed consent is obtained with specific attention to the unique complications associated with CPN/CPB. Patients initially are hydrated with 500 to 1000 mL normal saline solution to minimize the risk of hypotension. The procedure is performed using conscious sedation and noninvasive monitors with the patient in the left lateral decubitus position.

Linear EUS imaging from the posterior lesser curve of the gastric body allows identification of the aorta, which appears in a longitudinal plane. The aorta is traced distally to the celiac trunk, which is the first major branch below the diaphragm. The celiac plexus is not identified as a discrete structure but is located based on its position relative to the celiac trunk. Color Doppler can confirm the vascular landmarks. A 22-gauge needle (Wilson-Cook Medical Inc., Winston-Salem, N.C.; GIP Mediglobe, Tempe, Ariz.) is primed with saline solution and then placed through the biopsy channel and affixed to the hub. The needle is inserted under EUS guidance immediately adjacent and anterior to the lateral aspect of the aorta at the level of the celiac trunk (Fig. 7). The needle is flushed with 3 mL of normal saline solution to remove any tissue acquired during insertion. An aspiration test is performed to rule out vessel penetration before each injection. For CPN in pancreatic cancer patients, 10 mL (0.25%) of bupivacaine is injected, followed by 10 mL (98%) dehydrated alcohol. The alcohol, which
produces an echogenic cloud, may lead to discomfort despite sedation. Before withdrawing the needle, it should be flushed with 3 mL of normal saline solution to prevent seeding of the needle track with alcohol. The entire process is then repeated on the opposite side of the aorta. Occasionally, altered anatomy resulting from significant lymphadenopathy and/or bulky tumors may necessitate injection of the entire solution into one “unilateral” site. The efficacy of unilateral versus bilateral injection has never been formally studied. After the procedure, the vital signs are monitored for 2 hours. Before discharge, the blood pressure is checked in both a supine and erect position to assess for orthostasis. Celiac plexus neurolysis is routinely performed as an outpatient procedure, rarely necessitating hospitalization.

For CPB in patients with chronic pancreatitis, some physicians substitute a steroid (triamcinolone suspension 40 mg bilateral, 80 mg unilateral; Fujisawa USA, Deerfield, Ill.) in place of alcohol. Although use in patients with benign disease is controversial, the investigators administer a small volume of alcohol (4 mL bilateral, 8 mL unilateral), in addition to the steroid to increase the neurolysis. If alcohol, which is bactericidal, is not given along with the steroid, then the investigators recommend administering broad-spectrum antibiotics, particularly if the patient is receiving acid-suppressive therapy.

**OUTCOMES**

**Pancreatic cancer**

Wiersema and Wiersema\(^\text{30}\) published the initial study evaluating EUS CPN in 30 patients with malignancy, 25 with pancreatic cancer. The findings will not be reviewed because the same group published a follow-up study that included all 25 patients with pancreatic cancer from their initial report.\(^\text{31}\) This later prospective study involved 58 patients who underwent EUS CPN for pain secondary to inoperable pancreatic cancer. Neurolysis was performed by injecting 3 to 6 mL (0.25%) bupivacaine and 10 mL (98%) alcohol into both sides of the celiac region. Pain scores were assessed using a standardized 11-point visual analog scale. Forty-five patients (78%) experienced a drop in pain score after EUS CPN. The overall pain scores were significantly lower \((p < 0.0001)\) 2 weeks after the procedure. A multivariate analysis showed that patients found sustained pain relief for 24 weeks independent of morphine use or adjuvant therapy. However, patients who received chemotherapy alone or chemotherapy plus radiation had additional benefit. Pain relief resulting from adjuvant therapy increased over time and at 24 weeks was statistically significant \((p = 0.002)\). Although opioid administration increased throughout the study, the increase was not statistically significant. There were no major complications. Minor complications were mild and transient and included postural hypotension (20%), diarrhea (17%), and pain exacerbation (9%).

While this study offers preliminary data suggesting the efficacy and safety of EUS CPN, the small sample size, the absence of a placebo control group, and no physician or patient blinding limits the strength of the conclusions. Despite 45 patients (78%) experiencing a drop in pain score, only 31 (54%) experienced a decline of greater than 2 points, which is a measure of improvement that some consider necessary to signify efficacy. The benefit of EUS CPN diminished at 8 to 12 weeks, after which pain scores in patients not receiving adjuvant ther-
apy trended upward. While the results of this study are promising, these data, considered in isolation, do not allow us to make any definitive conclusions regarding the safety and efficacy of EUS CPN in pancreatic cancer.

**Chronic pancreatitis**

The efficacy of CPB for controlling the pain of chronic pancreatitis has not been established and most studies have yielded disappointing results.\(^{24-27}\) Gress et al.\(^{32}\) reported their initial experience using EUS CPB in 18 patients with chronic abdominal pain resulting from chronic pancreatitis that was unresponsive to pharmacologic and endoscopic therapy. They later updated their experience in 90 patients undergoing EUS CPB and included all patients from the initial report.\(^{33}\) Patients underwent EUS CPB with 10 mL (0.25%) bupivacaine and 3 mL (40 mg) triamcinolone on each side of the celiac plexus. In the initial phase of the study, patients were randomized to either EUS (n = 10) or CT-guided CPN (n = 8). A significant reduction in pain scores and narcotic use was seen in 50% of patients undergoing EUS CPB versus 25% undergoing CT-guided CPB. EUS CPB produced more protracted pain relief compared with CT-guided CPB, with 30% reporting improved symptom control at the end of the 24-week observation period.

When all 90 patients were considered, significant pain relief (defined by a decrease in pain score ≥3 on a visual analog scale of 0-10) was noted in 55% of patients at 4 and 8 weeks of follow-up (p ≤ 0.05). Persistent pain relief beyond 12 and 24 weeks was observed in 26% and 10% of patients, respectively. Patients over 45 years of age and those who had never undergone pancreatic surgery were more likely to experience pain relief. Mild transient diarrhea developed in 3 patients, and a peripancreatic abscess developed 5 days after EUS CPB in one. The investigators theorized the patient’s use of a proton pump inhibitor resulted in bacterial colonization of the stomach and subsequent transmural seeding. The abscess resolved with antibiotics alone. Their group now routinely administers prophylactic antibiotics to all patients undergoing CPB with steroids. A cost comparison determined that the cost per patient is lower with EUS versus CT guidance. They noted that 12 patients experienced a CPB with both EUS and CT guidance. Of these 12 patients, two thirds favored CPB under EUS guidance.

This study suffers from methodologic shortcomings that limit the strengths of the conclusions. The absence of a placebo group and nonblinded approach allows potential bias. Several other important details are lacking, including information concerning prior therapeutic interventions and details regarding narcotic use after EUS CPB. The finding that two thirds of patients prefer EUS versus CT guidance is of interest. However, although all 12 patients underwent CPB as a part of the study, only 3 of 12 underwent CPB with the alternate technique during the study period. The other 9 patients underwent CPB at least 6 months before enrollment. A comparison between two techniques performed remote in time does not allow a valid comparison of patient preference. The method for performing the cost analysis is not clearly stated and appears oversimplified because it does not consider longitudinal use of other health care resources.

**INDICATIONS**

There are several potential advantages of using EUS versus PQ guidance for performing CPN/CPB. The proximity of the posterior lesser curve of the stomach to the celiac plexus, use of continuous real-time visualization of the target area, and availability of Doppler to assess the vasculature all facilitate accurate needle placement. By doing so, EUS theoretically may improve pain relief and reduce complications. Unfortunately, the lack of well-designed comparative studies between EUS and PQ approaches prohibits verification of these assumptions. Furthermore, no study has demonstrated conclusively the anatomic spread of the injected agent during EUS CPN/CPB.

On initial review, it appears that EUS CPN/CPB has been evaluated in four studies. Closer inspection clarifies that two of these trials are simply updated data from initial pilot studies. Only two studies have been conducted, one each for CPN in pancreatic cancer and CPB in chronic pancreatitis. Although the results of these two studies are encouraging, they too suffer from methodologic shortcomings that limit the strength of the conclusions. In addition, both studies were conducted by expert endosonographers. One must assume that as use of this method broadens, so too will the reported rate of complications and potential for diminished efficacy. Those who perform this procedure should have a thorough knowledge of relevant anatomy, mechanism of action, and technical aspects concerning linear EUS, color Doppler, and aspiration needles. This level of expertise is necessary to optimize the efficacy and minimize complications.

Despite shortcomings in the publications, our review of the data leads us to the following conclusions:

1. The efficacy of CPN/CPB is similar regardless of the technique (EUS or PQ). This view is supported by the finding of a meta-analysis, which concluded that the efficacy of CPN was inde-
dependent of the PQ approach or use of radiologic guidance.16 The reported efficacy rates of EUS CPN have been similar to those reported for PQ methods. Although comparative studies have not been performed, the investigators suspect that the efficacy is similar.

2. The neurologic risk of EUS CPN/CPB is similar or slightly lower than PQ methods. Serious neurologic complications (such as paraplegia) have not been reported with EUS CPN/CPB. This may in part arise from the limited experience with EUS CPN/CPB versus PQ methods. However, EUS is an “anterior” approach and thereby avoids the retrocrural space and may reduce this risk of neurologic dysfunction and pulmonary complications. Furthermore, as opposed to the PQ anterior approach, with EUS, the needle only traverses the gastric wall, presumably eliminating complications resulting from inadvertent penetration of surrounding organs. The investigators assume that the risk of local pain, hypotension, and diarrhea would be similar for EUS and PQ approaches. The nonsterile transgastric approach used with EUS CPN/CPB may increase the risk of infection, particularly when a steroid is used as the blocking agent.

If EUS guidance offers no advantage in terms of pain relief, and no, to minimal, risk advantage, then what is the role versus PQ techniques?

Pancreatic cancer

The major disadvantage with EUS CPN is the inherent cost associated with the endoscopy and conscious sedation. Also, when a diagnostic block is desired, the necessary conscious sedation will confound the assessment of any benefit derived from injection of the local anesthetic. Given the inaccuracies of a diagnostic block, few consider this an issue.7,17,34 Furthermore, the use of conscious sedation alleviates acute discomfort associated with CPN. The ability to perform EUS CPN at the time of tumor biopsy and staging combines diagnostic and therapeutic modalities, simplifies patient care, and may reduce cost. The investigators reserve EUS CPN for patients undergoing EUS for another reason, such as diagnosis or staging, for poor operative candidates, or those in whom disease spread precludes a satisfactory PQ approach. The timing of the block relative to the onset of pain may predict response. In one study, CPN was more effective when performed early after pain onset instead of late in its course.7 This may be explained by the fact that early pancreatic cancer pain appears to derive mainly from the celiac plexus.

Although most studies have found that CPN reduces cancer pain, it rarely eliminates pain, and nearly all patients require continued opioid use, albeit often at a lower dose. When counseling patients, it is important to emphasize a realistic goal, which is not to eliminate pain but to optimize oral pharmacologic therapy and to allow a dose reduction to minimize the side effects.

Chronic pancreatitis

Most studies of PQ CPB in chronic pancreatitis have shown minimal efficacy.24-27 In a retrospective study of PQ CPB with steroids, pain relief was only experienced in those who had not yet developed narcotic dependence.55 As a result, some recommend EUS CPN early in the disease course.36 However, inconsistent findings among studies, short-term pain relief even among those who respond, and the risks of repeated block, which includes retroperitoneal fibrosis tempers this approach.37 Others perform EUS CPB in patients with chronic pancreatitis and intractable, constant abdominal pain.33 Benefit in these patients is limited.

The investigators summarize, using the classification system (Table 1) and definitions for level of evidence (Table 2) adopted by the American Heart

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<th>Table 1. Classification system38</th>
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<td><strong>Class I</strong> Conditions for which there is evidence or general agreement that a given procedure or treatment is useful and effective.</td>
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<td><strong>Class II</strong> Conditions for which there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.</td>
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<td><strong>Class IIa</strong> Weight of evidence/opinion is in favor of usefulness/efficacy.</td>
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<td><strong>Class IIb</strong> Usefulness/efficacy is less well established by evidence/opinion.</td>
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<tr>
<td><strong>Class III</strong> Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.</td>
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<th>Table 2. Level of evidence38</th>
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<td><strong>Level of evidence A</strong> Data derived from multiple randomized clinical trials</td>
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<td><strong>Level of evidence B</strong> Data derived from a single randomized trial or non-randomized studies</td>
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<td><strong>Level of evidence C</strong> Consensus opinions of experts</td>
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<th>Table 3. Recommendations and strength of evidence for using EUS CPN and EUS CPB38</th>
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<td><strong>Class of recommendation</strong></td>
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Association, the data as follows (Table 3). The investigators consider pancreatic cancer pain a Class IIa indication because the weight of evidence favors the efficacy of EUS CPN. However, the paucity of studies and sound data leave us to consider chronic-pancreatitis-induced pain a Class IIb indication. In both cases, the level of evidence is category B.

The only absolute contraindications for EUS CPN/CPB are the following: (1) uncertainty regarding the diagnosis, (2) coagulopathy (INR >1.5), (3) thrombocytopenia (platelets <50,000), or (4) an uncooperative patient. Relative contraindications include altered anatomy prohibiting access or a history of multiple prior CPBs in patients with chronic pancreatitis.

In summary, despite the paucity of data, EUS CPN appears to be as effective and as safe as other methods of CPN for providing pain relief from pancreatic cancer. The EUS approach may be the most cost effective if CPN is performed at the time of biopsy and staging. Data for EUS CPB in chronic pancreatitis is conflicting, and, regardless of technique, CPB should be considered investigational and only advocated as part of a clinical trial. Patients should be made aware of the uncertain benefit and potential risks.

Larger long-term, prospective, randomized, double-blind, placebo, controlled trials that evaluate cost, clinical outcomes, and quality of life are needed. Only then can the investigators verify the efficacy and safety of EUS CPN/CPB and identify advantages and disadvantages of this approach over conventional techniques. Future trials should focus on remaining issues, including the following: (1) optimal timing and route for CPN/CPB, (2) ideal composition of the injected agent, (3) relative cost, (4) patient preference, (5) influence on quality of life, (6) effect on hospitalization duration (in those with chronic pancreatitis), and (7) potential survival advantage (in patients with pancreatic cancer).

REFERENCES


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