Role of Endoscopic Ultrasonography Guided Celiac Plexus Neurolysis in the Management of Pancreatic Cancer Pain

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ABSTRACT:

BACKGROUND:

Celiac plexus neurolysis (CPN), a chemical splanchnicectomy of the celiac plexus, is used to treat pain caused by pancreatic cancer. Originally performed by anesthesiologists and radiologists via a posterior approach, recent advances in endoscopic ultrasonography (EUS) have made this technique an attractive alternative. EUS guided celiac plexus neurolysis (CPN) is simple to perform and avoids serious complications such as paraplegia or pneumothorax that are associated with the posterior percutaneous approach.

OBJECTIVE:

To assess the efficacy and safety of EUS guided celiac plexus neurolysis in the management of pain caused by pancreatic cancer.

METHODS:

This study included (310) patients with painful and inoperable pancreatic cancer were submitted to EUS guided celiac plexus neurolysis (CPN) at a tertiary referral center. The following data were collected: age, gender, tumor location, vascular invasion, adjuvant therapy, and laboratory tests including prothrombin time, and complete blood counts were obtained at baseline (before EUS celiac plexus neurolysis).

RESULTS:

Of 310 procedures performed, 217(70%) patients develop immediate and complete pain relieves (within 24 hours of procedure) and no need for narcotic analgesia during follows up (12 weeks). Sixty-one (20%) patients had partial response to the procedure (decreasing in the need for narcotic analgesia during follow up). Thirty-two (10%) patients were lost to follow up and no outcome of procedure obtained.

CONCLUSION:

EUS is more safe, feasible, and more effective than other methods in performing CPN and controls pain caused by unresectable pancreatic cancer.

KEY WORDS: endoscopic ultrasound guided celiac plexus neurolysis, pancreatic cancer, and abdominal pain.

INTRODUCTION:

Pancreatic cancer is the tenth most common malignancy and the fourth cause of cancer-related death worldwide. Because 5-year survival in referral centers is less than 30%, clinical management of most patients involves palliation of the symptoms of which 90% are weight loss, jaundice, and pain.[1]

While jaundice related to biliary obstruction can be palliated by means of endoscopic therapy or surgery, pancreatic pain is often difficult to control. Initial therapy with non-steroid anti-inflammatory agents (NSAIDs) is often rapidly overwhelmed by pain and necessitates being associated with opioid administration.[2]

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Celiac plexus neurolysis (CPN) affords effective pain control in patients with pancreatic cancer and is not associated with opioid side effects. CPN is a chemical splanchnicectomy of the celiac plexus that ablates the afferent nerve fibers that transmit pain from intra-abdominal viscera. CPN is most commonly used to palliate patients with pain from pancreatic cancer and can be performed percutaneously, surgically, or under EUS guidance. The most common approach is to use a percutaneous route to inject absolute alcohol into the celiac plexus under fluoroscopic or CT guidance[3].

The CPN technique was first described by Kappis *et al.* in 1919[3]; since then, a number of modifications have been proposed and introduced in a clinical setting in an attempt to improve the

accuracy of needle placement and pain relief while reducing procedure-related complications. Nowadays, CPN is most commonly used to palliate patients suffering from pain due to pancreatic cancer and chronic pancreatitis; it can be performed using different approaches either percutaneously, surgically or under EUS guidance. Until the 1990s, the most common of the above was surely the percutaneous route, injecting absolute alcohol into the celiac plexus under fluoroscopy or CT guidance. Up to 1% of patients undergoing percutaneous CPN may have serious complications develop, including lower extremity weakness, paresthesias, epidural anesthesia, , and pneumothorax[4].Theoretically, EUS CPN may be safer than posterior percutaneous techniques because EUS allows direct access to the celiac plexus without risk to vital spinal nerves, the diaphragm, or spinal arteries[5]. Additionally, staging and fine needle aspiration (FNA) of the tumor can be performed at the same procedure.

Endoscopic ultrasonography (EUS) is a relatively new imaging technique which couples a high frequency ultrasound probe with an oblique viewing endoscopic instrument. This combination allows the endoscopist to obtain a perfect evaluation of the pancreatic parenchyma and surrounding structures, not least, the aorta and celiac trunk. This imaging modality has achieved wide acceptance as the technique of choice for the evaluation of pancreatic disease, diagnosis and staging of pancreatic cancer, diagnosis of idiopathic pancreatitis and the evidencing of neuro-endocrine neoplasms[6].

This innovation has opened the field of operative EUS, allowing the possibility of following, under real time guidance, any kind of device passed throughout the working channel to reach a target lesion. Since that time, EUS has been tested in this new operative setting for many reasons, mainly the cytological analysis of tumors and, more recently, it has been applied in the treatment of pain in patients with chronic pancreatitis or pancreatic cancer by injecting neurolytic agents in the area of the celiac plexus[7].

In theory, EUS CPN is safer than posterior percutaneous techniques because EUS allows direct access to the celiac plexus without risk to the vital spinal nerves, the diaphragm or the spinal arteries[8]

The aim in the current study is to evaluate the safety and efficacy of EUS CPN for the palliation of patients with pancreatic cancer pain.

PATIENTS AND METHODS:

PATIENTS:

From March 2002 to February 2008, 322 patients with upper abdominal pain that was related to suspected or known pancreatic malignancy and that required treatment with narcotic analgesics were offered EUS CPN. The potential risks of the procedure (hypotension, diarrhea, neuropathic pain, paraplegia, and endoscopic complications) were discussed with each patient, and signed informed consent was obtained. All patients underwent the EUS procedure at Gastroenterology and Hepatology teaching Hospital-Baghdad as a tertiary referral center. EUS CPN was performed if malignancy was present and if vascular invasion by established EUS criteria (loss of hyperechoic margin between the tumor and the involved vessel) precluded surgical resection[1], or the patient was not considered a candidate for surgery because of other concurrent disorders. The diagnosis was confirmed by EUS by using EUS criteria (hypoechoic mass like lesion with ill defined margin involving the pancreatic parenchyma) and FNA when a tissue diagnosis was not available before EUS. Of the 322 patients considered for the procedure, 310 had a diagnosis of pancreatic cancer not amenable to surgical resection and underwent EUS CPN during the same EUS procedure or in other sessions. Twelve patients were excluded because of the finding of a surgically resectable lesion.

Technique:

Nearly all procedures were performed on an outpatient basis with discharge on the same day. Patients were hydrated with intravenous normal saline solution (250 mL-500 mL) before the procedure. Baseline laboratory tests included prothrombin time and complete blood count. No patient had prolongation of the prothrombin time (>18 seconds) or thrombocytopenia (<80,000 platelets/mL) sufficient to necessitate exclusion. Patients were placed in the left decubitus position and were sedated by using of midazolam or pehtidin administered intravenously.

EUS CPN was performed with a linear array echoendoscope (FG-34UX or FG-38UX, Pentax and Hitachi ultrasound EUB 525) by single well expert endosonographer. In brief, sagittal views of the aorta were obtained through the posterior gastric wall. Then, the aorta was traced to the celiac trunk. In few patients the ganglion is visualized as a discrete structure by EUS, but in the majority of patients is identified by its position relative to the celiac artery. The right celiac

ganglion is most commonly located 6 mm inferior to the celiac artery origin and the left ganglion is most commonly located 9 mm inferior to the origin. Under direct EUS visualization, a 22 to 23 gauge, 4 to 8 cm aspiration needle (Wilson-Cook Medical, Inc. Winston-Salem, N.C.) primed with normal saline solution was placed immediately adjacent and anterior to the lateral aspect of the aorta at the level of the celiac trunk. After injecting 2 mL of saline solution to clear the needle, an aspiration test was performed. If no blood was obtained, 5 mL of 0.25% preservative-free xylocain was injected. The aspiration test was repeated, and if there was no blood return, 10 mL of dehydrated 98% absolute alcohol was injected. The needle was then flushed with 3 mL of saline solution and withdrawn from the patient. Endosonographically, an echo-dense cloud was typically identified with alcohol injection. The process was then repeated on the opposite side of the aorta. The average estimated time for the EUS CPN portion of the procedure was 10-15 minutes. After the procedure, blood pressure was checked in the supine and erect positions to assess for orthostasis, and the abdomen was examined for signs of peritonitis before discharge (recovery time, approximately 2 hours). Complications were recorded and the patient was reevaluated for complications at 2 and 7 days after the procedure.

Follow up:

Pain relief was defined as absence or decrease in the feeling for pain immediately after the procedure and decrease in the narcotic usage[4]. These patients were followed up weekly for 12-24 weeks for assessing response of pain to the procedures.

RESULTS:

The studied patients consisted of 198 (64%) men and 112 (36%) women (mean age 55 years; range 35 to 76 years). Of the 310 patients enrolled, 161 (52%) had the tumor located in the head of the pancreas, 89 (28%) in the body, 60 (19%) the tail. Overall, 63% of the patients had portal venous invasion, 20% had major arterial or mesenteric venous invasion, 12% had invasion of adjacent organs (stomach or duodenum), and 28% had distant metastasis (liver and mediastinal masses) based on EUS and CT scanning findings. EUS-FNA was performed in 273 patients; diagnostic material was obtained in 262 (95% sensitivity) who underwent EUS CPN later on. After EUS CPN, 77 (24%) patients received chemotherapy (5-fluorouracil). Thirty-eight (12%) and 103(33%) patients with obstructive jaundice underwent triple bypass surgery and endoscopy guided stent insertion respectively, to relieve obstruction.

Of 310 procedures performed, 217(70%) patients developed immediate and complete pain relieve (within 24 hours of procedure) and no need for narcotic analgesia during follow up (12 weeks). Sixty-one (20%) patients had partial response to the procedure in the form of decreasing in the need for narcotic analgesia (Tramadol) from 100-200mg/daily to 50mg/daily or on need during follow up. The two-tailed P value equals (0.0024) is considered to be statistically significant. Thirty-two (10%) patients were lost to follow up and no outcome of procedure obtained.

Complications:

There were no major complications and no patient was hospitalized after an outpatient procedure. Eleven patients had transient abdominal pain after the procedure, which persisted less than 48 hours and was relieved by an increase in the dosage of pain-killer medication. A fall in the systolic and diastolic blood pressure by 10% to 15% for less than 30 minutes occurred in 30% of the patients after EUS CPN, but all responded to an increase in the rate of intravenous fluid administration. Diarrhea, characterized by more frequent stools for less than 48 hours, was noted in 20 patients. All episodes responded to antidiarrheal agents.

Table (1): Patients Characteristics

Variable	No. (%)	Mean(Range)
Patients enrolled	310	
Male	198(64%)	
Female	112(36%)	
Age(Y)		(55) 35 -76

Table (2): Tumor Location in the pancreas

Location	No. (%)
Head	161(52%)
Body	89 (28%)
Tail	60 (19%)

Table(3): Tumor invasion and metastasis

Tumor invasion and metastasis	No. (%)
Portal Vein	195(63%)
Mesenteric vessels	62(20%)
Locoregional invasion	37(12%)
Distant metastasis	86(28%)

Table (4): Follow up of response to EUS-CPN

Patients	Follow up	
	Up to 12 Weeks	> 12 Weeks
Complete response 217(70%)	No need for narcotic analgesia	33/217(15%)developed mild pain- relieved by simple analgesia
Partial response 61(20%)	Decrease in the doses of narcotic analgesia to the half or less	24/61(39%) developed increasing pain-increasing the dose of narcotics

DISCUSSION:

More recently, EUS-guided CPN was reported as a safe and effective pain management modality in pancreatic cancer patients[4]. In a small study of 25 patients with pancreatic cancer who underwent EUS-guided CPN, pain relief was obtained in 88% of patients, for a median duration of 10 weeks[5]. In a larger prospective study 14 of 58 patients with painful and inoperable pancreatic cancer, pain sensation were significantly lower at 2 weeks after EUS-guided CPN, and the effect was sustained at 24 weeks when adjusted for morphine use and adjuvant therapy. Of the 58 patients, 45 were noted to have reduced pain sensation. Five patients had transient abdominal pain, 12 patients had hypotension that responded to fluids, and 9 patients had transient diarrhea that was treated with antidiarrheals[7].

In a prospective randomized study of 3 techniques for posterior CPN in 61 patients, Ischia et al noted that 60% to 75% of patients with pain were palliated until death irrespective of the technique used[9]. Eisenberg et al concluded that CPN was effective in reducing pain in 70% to 90% of patients regardless of the technique used (CT or fluoroscopy)[4]. These data suggest that CPN is effective irrespective of the method of needle guidance.

The data of this study is similar to the results of other studies using EUS guided CPN[2,4,5] .EUS CPN in this large present study was associated with a decrease in pancreatic cancer pain. EUS CPN effectively reduced pain in 90% patients. Our study found that CPN performed under EUS guidance appears to be as effective as CPN performed with other techniques.

The timing of the block relative to the onset of pain appears to be an important predictor of response. Ischia et al found CPN to be more effective when the block was performed soon after onset rather than late in the course of the disease[9]. Early in the course of pancreatic cancer, the associated pain appears to derive mainly from the celiac plexus,

whereas pain during the terminal stages of the disease may also arise from involvement of other visceral and somatic nerves[7]. This explains the complete response of pain to the EUS-CPN in the majority of patients included in this study in the first 12 weeks while the pain that developing during follow up were most probably due to direct tumor extension to the adjacent viscera. In this study the EUS guided CPN was done once the patient complaining from pain and proved to have unresectable pancreatic cancer.

We consider EUS-guided CPN an effective way to relieve pain from pancreatic cancer and believe that it offers advantages over other techniques. Both surgery and EUS provide direct access to the celiac plexus, but since EUS is less invasive, there are fewer complications[10]. Preoperative detection and tissue diagnosis of pancreatic cancer are a routine part of the index EUS examination. If tissue diagnosis can be obtained during the procedure, CPN can be completed at the same time. The proximity of the celiac ganglia to the gastric wall ensures accurate placement of neurolytic agents while minimizing potential sequelae. With its anterior approach, the EUS method avoids traversing posterior structures, reducing the chance of their injury[11, 12]. Because of the inherent costs of conscious sedation and the endoscopic procedure itself, the cost-effectiveness is most enhanced when the procedure is performed at the time of diagnostic EUS-guided fine-needle aspiration; the added benefit is a reduced number of procedures for patients[13]. The morbidity of EUS-guided CPN is low, and there has been no reported mortality. Thus, use of EUS-guided CPN should be considered and performed relatively early in the course of disease to offer optimal pain relief and increase the patient's quality of life[14].

The limitations of this study are difficulties in quantifying pain, which is a variable and subjective experience.

There were no serious complications in the present study. However, 5 patients (0.2%) experienced transient increases in pain for up to 24 hours. The pain was likely caused by irritation of the celiac ganglion, adjacent retroperitoneum by alcohol, or both. In all patients the pain was managed with analgesics and no further evaluation was performed.

CONCLUSION:

EUS CPN appears to be more safe, feasible and effective than other methods for performing CPN. EUS CPN for pancreatic cancer pain may be the most cost-effective of all CPN techniques, because tumors can be staged and biopsied at the time of CPN.

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