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How to Improve the Efficacy of Endoscopic Ultrasound-guided Celiac Plexus Neurolysis in Pain Management in Patients With Pancreatic Cancer: Analysis in a Single Center

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Abstract: Visceral pain secondary to pancreatic cancer is often difficult to control and poses a challenge to the physician. We retrospectively analyzed the efficacy and safety of endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN) in patients with unresectable pancreatic cancer. Forty-one patients with severe pain despite treatment with opioids underwent EUS-CPN with absolute alcohol. Patients scored their pain on a scale of 0 to 10 and were interviewed after the procedure. Of the 41 patients, 33, 37, and 25 patients reported improvement in their pain within 3 days, at 1 week, and at 3 months, respectively, following the procedure. Of all the patients, 19 patients reported substantial improvement and 4 patients showed complete disappearance of pain. Complication appeared in 2 patients with transient hypotension. In our study, EUS-CPN is a safe and effective form of treatment for intractable pain secondary to advanced pancreatic cancer.

Key Words: EUS-CPN, pancreatic cancer, pain control

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Pancreatic cancer is a fatal gastrointestinal cancer and its morbidity has increased over the past few decades. Fewer than 30% of patients are considered operable at diagnosis because of its highly malignant characteristics of invasive growth and early metastasis,[1] and the overall 5-year survival rate is still around 5%.[2] Visceral pain is present in over 70% of patients at the time of diagnosis of pancreatic cancer[3,4] and gradually increases to a level that is difficult to control; this constitutes the most important and challenging goal of palliative care. Despite the availability of improved nonsteroidal anti-inflammatory drugs and opioid analgesics, a high dose of such drugs still cannot provide adequate analgesia, and many adverse effects are also observed.[5] Thus, a more efficient form of pain management, such as interventional methods, is essential for such patients.[6]

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Visceral pain secondary to pancreatic carcinoma is mediated by sympathetic nociceptive afferent fibers from the pancreas and is relayed through the celiac plexus to the splanchnic nerves and finally affects the spinal cord.[7] Some chemical agents such as alcohol can be used to block the nerve impulse, thus acting as an analgesic. Celiac plexus neurolysis (CPN) is defined as permanent ablation of the celiac plexus neurons by the injection of neurolytic agents, either phenol or alcohol. Since its establishment, CPN has been performed percutaneously under fluoroscopic or computed tomography guidance. However, randomized controlled studies on CPN and some recent meta-analyses have indicated its relatively high rate of serious adverse effects, including lower extremity paresthesia and paralysis.[4,7]

In recent times, endoscopic ultrasound (EUS) has been combined with high-resolution ultrasound and endoscopy. It is commonly used to perform EUS-guided fine-needle aspiration (EUS-FNA) cytology of pancreatic masses to diagnose pancreatic cancer. During the same endoscopic procedure, it can also be used to perform EUS-guided celiac plexus neurolysis (EUS-CPN) in patients with severe pain arising from pancreatic cancer. Under EUS guidance, critical anatomy markers can be identified clearly, and neurolytic substances can be injected precisely and safely into the celiac plexus area.[8,9] In previous studies, EUS-CPN displayed both optimistic results and an excellent safety profile, which indicates that it is a promising method. However, controversy continues to surround some methodological issues related to EUS-CPN, and some potential analgesic characteristics of EUS-CPN still need to undergo further study.

We aimed to assess the efficacy of EUS-CPN for pain management in patients with unresectable pancreatic cancer in a single institute and report certain analgesic characteristics of EUS-CPN.

MATERIALS AND METHODS

This study is a result of a retrospective analysis of a prospectively collected database study conducted in Huashan Hospital, Shanghai, China, catering to the Chinese population. This protocol was approved by the Institutional Review Board of Huashan Hospital. Patients who were admitted to Huashan Hospital between September 2009 and December 2012 were selected.

The inclusion criteria were as follows: (1) age older than 18 years; (2) enduring abdominal or back pain due to confirmed pancreatic cancer (surgical biopsy or EUS-FNA); (3) presence of unresectable pancreatic cancer (distant metastasis; the invasion of celiac trunk or superior mesentery

artery) or intolerability to surgery because of other systemic disorders; (4) an ineffectual ladder approach to pain management beginning with nonsteroidal anti-inflammatory drugs followed by escalating doses; and (5) informed consent.

Before the EUS-CPN procedure, the following data were collected by authorized staff from each patient: age, sex, tumor location, tumor size, TNM staging, pain duration before the procedure, the dose of oral opioids, and visual analog scale pain score.

Patients underwent EUS-CPN with a curved linear-array video echoendoscope (EG-530UT, SU-7000 system; Fujifilm, Japan). If the pancreatic cancer in the patient was considered unresectable before the procedure, EUS-FNA was performed preferentially. The celiac plexus was identified as the area following the aorta to the origin of the celiac trunk (Fig. 1), and alcohol was injected into the celiac plexus area. If the celiac ganglia were visualized under linear EUS (Fig. 2), the injection was applied directly into the ganglia (EUS-CGN). A total of 10 ml of 2.5% bupivacaine followed by 20 mL absolute alcohol was injected into the celiac plexus area or directly into the ganglia using a 22-G needle (EchoTip ECHO-3-22; Cook Medical). When alcohol was injected into each patient, a dense hyperechoic cloud in the area of injection was observed (Fig. 3). Each patient was given intravenous infusion of Ringer lactate during the procedure to prevent hypotension, and blood pressure was monitored afterward.

Pain improvement was evaluated after 3 days, at 1 week, and at 3 months after the CPN procedure. The same authorized staff collected the following information: (1) the visual analog scale pain score; (2) the weekly amount of pain medication consumed; (3) whether the EUS-CPN helped relieve pain (yes/no); and (4) whether the pain had returned to baseline (yes/no).

Definition

In the study, pain relief was defined as a numeric rating scale pain score of ≤ 3 or a $\geq 30\%$ reduction in baseline pain without an increase in pain medication usage. A complete response was defined as a reported pain score of 0 for 3 consecutive weeks without an increase in pain medication. Treatment failure was defined as absence of pain reduction or pain medication usage 1 week after the EUS-CPN procedure. Onset of pain relief was defined as time until pain relief was experienced and was calculated from the date of CPN until the date of apparent reduction in the patient's pain score to at least 30% of the baseline pain score. If the patient suffered treatment failure, onset of pain relief was recorded as 0 day. Duration of pain relief was defined as time from the date of onset of pain relief to the date the patient's pain had returned to within 30% of the baseline level. If at the endpoint of follow-up (3 mo) the patient still experienced pain relief, the duration of pain relief was recorded as 3 months.

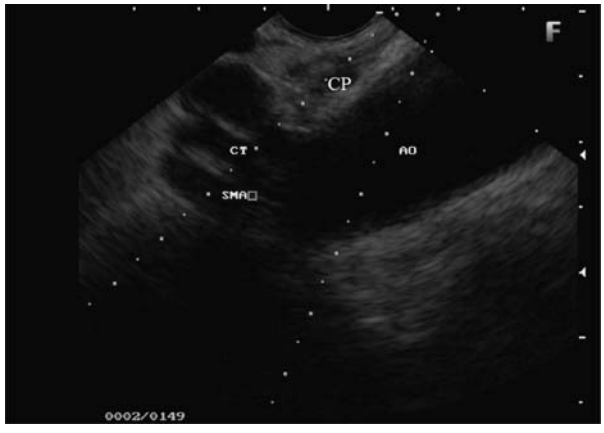

FIGURE 1. EUS imaging of the location of the celiac plexus. The image shows that the CP is located in the area between the AO and the CT. AO indicates aorta; CP, celiac plexus; CT, celiac trunk; EUS, endoscopic ultrasound; SMA, superior mesenteric artery.

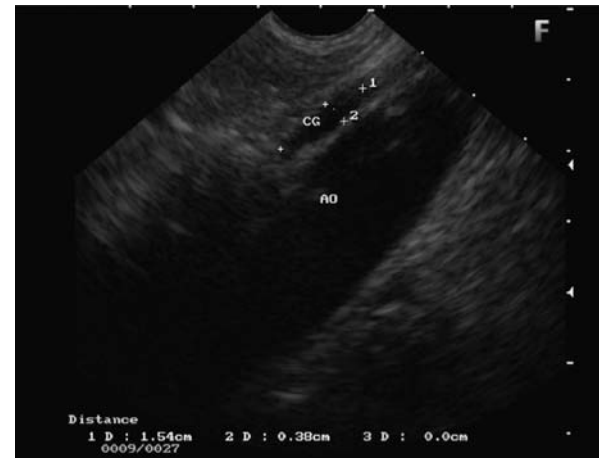

FIGURE 2. EUS imaging of the location of the celiac ganglia. The image shows the location and size of the CG. AO indicates aorta; CG, celiac ganglia; CT, celiac trunk; EUS, endoscopic ultrasound; SMA: superior mesenteric artery.

RESULT

Forty-one patients were enrolled from September 2009 to December 2012. Patient demographics, tumor size, tumor location, and TNM staging are reported in Table 1. The average baseline pain score before the procedure was 7.4 (range, 5 to 10), and the duration of pain before CPN was about 3.26 months (range, 1 to 7 mo). After EUS-CPN, pain relief was observed in 33, 37, and 25 patients within 3 days, at 1 week, and at 3 months, respectively. Of them, 19 patients reported substantial improvement (pain score decreased $>50\%$), 4 patients showed complete response, and 2 patients suffered treatment failure. The overall average onset of pain relief was 4.23 days (range, 1 to 9 d), and the average duration of pain relief was 2.43 months (range, 0.5 to 3 mo). Two patients died before the last follow-up because of disease progression. Complication appeared in 2 patients with transient hypotension. No statistical differences were observed between subgroups in terms of age, sex, and tumor location. EUS-CPN was more efficient in patients with larger tumor and lymph node metastasis (Table 1).

Pain Duration Before EUS-CPN

The overall average duration of pain before CPN was about 3.26 months. Of the 41 patients, 25 patients suffered from pain for <3 months, whereas 16 patients suffered for >3 months. The result indicates that patients with short-term pain had significantly efficient outcomes compared with patients with long-term pain. The onset of pain relief showed no statistical difference between the 2 groups;

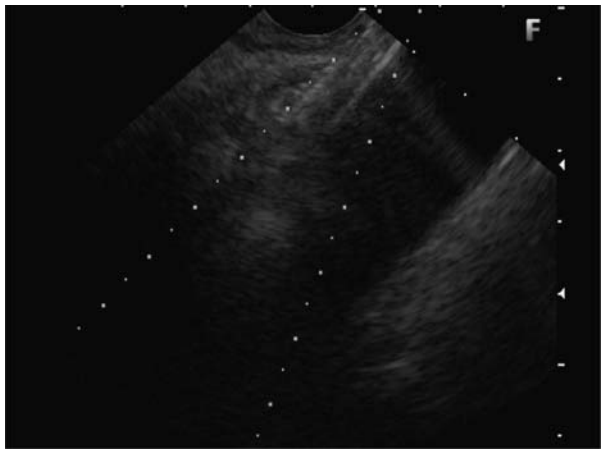

FIGURE 3. EUS imaging of the EUS-CPN injection. EUS-CPN indicates endoscopic ultrasound-guided celiac plexus neurolysis.

however, patients with short-term pain experience longer duration of pain relief (Table 2).

Pain Score Before EUS-CPN

The average baseline pain score before the procedure was 7.4. Of the 41 patients, 28 patients had a pain score ≤ 7, whereas 13 patients had a score > 7. Patients with a high score showed significantly visible pain relief compared with those with low scores in 3 days and 1 week after EUS-CPN; however, the pain relief in these patients was poorer at 3 months after the procedure and they experienced longer onset of pain relief (Table 2).

Injection Area of the EUS-CPN

Of the 41 patients, 15 patients underwent EUS-CPN, whereas EUS-CGN was performed in the remaining 26 patients. The results of the 2 groups in the short time after the procedure show no statistical difference. The EUS-CGN group experienced greater pain relief within 3 months after the procedure, lower treatment failure rate, shorter duration for onset of pain relief, and longer duration of pain relief (Table 2).

DISCUSSION

Given the dismal prognosis of inoperable pancreatic cancer and potential for intractable, narcotic-dependent pain, any low-risk therapy that may mitigate these symptoms is likely to have an important role in patient management. CPN was performed percutaneously in the early decades after its introduction. However, it was gradually substituted by EUS guidance because of difficulty of locating the celiac plexus, leading to some lethal complications.

The first EUS-CPN was performed by Wiersema and Wiersema in 1996, demonstrating high efficacy in patients with advanced abdominal malignancy with low morbidity.[10] Subsequent studies confirmed these findings, and, in a meta-analysis of EUS-CPN studies with varying length of follow-up, pain reduction was observed in approximately 80% of patients.[8]

In our study, the overall effectiveness was observed at around 80%, which is similar to the observation in other studies.[11–14] There is no significant correlation between the efficacy of EUS-CPN and age, sex, and tumor location of patients. However, we discovered that the bigger tumor size and later staging lead, especially in the case of positive lymph node metastasis, to poor effectiveness. It may be easy to comprehend that, with the tumor progressing, the scope of neural invasion expanding, and the level increasing, the pancreatic cancer was more tolerable to analgesic treatment.

TABLE 1. The General Characteristics of Patients and its Relationship with the Efficacy of EUS-CPN

Subject Characteristics	n	N (%)			Onset of Pain Relief (d)	Duration of Pain Relief (mo)	*P*
		3 d	1 wk	3 mo			
Age (y)							
≤60	19	15 (78.95)	17 (89.47)	12 (63.16)	4.11	2.54	0.0976
> 60	22	18 (81.81)	20 (90.91)	13 (59.09)	4.29	2.37	
Sex							
Male	24	19 (79.17)	22 (91.67)	15 (62.5)	4.01	2.16	0.1032
Female	17	14 (82.35)	15 (88.26)	10 (58.82)	4.92	2.74	
Tumor location							
Head	5	4 (80.00)	4 (80.00)	2 (40.00)	4.18	2.08	0.0729
Neck	5	4 (80.00)	5 (100.00)	3 (60.00)	4.25	2.39	
Body	16	13 (81.25)	14 (87.5)	11 (68.75)	4.32	2.57	
Tail	15	12 (80.00)	14 (93.3)	9 (60.00)	4.09	2.54	
Tumor size (diameter, cm)							
≤2	3	3 (100.00)	3 (100.00)	3 (100.00)	4.46	3.00	0.0305
> 2, ≤ 4	16	14 (87.50)	16 (100.00)	10 (62.50)	4.36	2.51	
> 4	22	16 (72.73)	21 (81.82)	12 (54.55)	3.53	1.84	
TNM staging							
T3NxMx	7	5 (71.43)	7 (100.00)	5 (71.43)	4.02	2.89	0.0229
T4NxMx	34	28 (82.35)	30 (88.23)	20 (68.82)	5.04	1.99	
TxN0Mx	10	7 (70.00)	8 (80.00)	8 (80.00)	4.34	2.94	0.0147
TxN1Mx	31	26 (83.87)	29 (93.55)	17 (54.84)	4.30	2.19	
TxNxM0	14	10 (71.43)	11 (78.57)	8 (57.14)	3.74	2.85	0.0588
TxNxM1	27	23 (85.19)	26 (96.30)	17 (62.96)	4.88	2.31	

EUS-CPN indicates endoscopic ultrasound-guided celiac plexus neurolysis.

TABLE 2. The Relative Factors Affecting the Efficacy of EUS-CPN

Relative Factors	n	N (%) 3 d	1 wk	3 mo	Completely Pain Relief	Treatment Failure	Onset of Pain Relief (d)	Duration of Pain Relief (mo)
Pain duration before EUS-CPN								
≤3 mo	25	21 (84.00)	24 (96.00)	17 (68.00)	3 (12.00)	0 (0.00)	4.11	2.81
> 3 mo	16	12 (75.00)	13 (81.25)	8 (50.00)	1 (6.25)	2 (12.50)	4.39	1.39
P		0.0377	0.0419	0.0201	0.0197	0.0017	0.0821	0.0231
Baseline VAS scores								
≤7	28	22 (78.57)	25 (82.29)	19 (67.86)	3 (10.71)	2 (7.14)	5.69	2.55
> 7	13	11 (84.62)	12 (92.31)	6 (46.15)	1 (7.69)	0 (0.00)	2.03	2.14
P		0.0250	0.0571	0.0313	0.0218	0.0008	0.0227	0.0696
Injection area of EUS-CPN								
EUS-CPN	15	12 (80.00)	14 (93.33)	8 (53.33)	1 (6.67)	2 (13.33)	5.52	1.94
EUS-CGN	26	21 (80.77)	23 (88.46)	17 (65.38)	3 (11.54)	0 (0.00)	3.94	2.89
P		0.0983	0.0682	0.0414	0.0392	0.0047	0.0416	0.0072

EUS-CGN indicates endoscopic ultrasound-guided celiac ganglia neurolysis; EUS-CPN, endoscopic ultrasound-guided celiac plexus neurolysis; VAS, Visual Analog Scale.

More than 80% of patients benefited from EUS-CPN within 1 week, which resulted from nerve fiber demyelination caused by ethanol, and about half of the patients continued to experience pain relief at 3 months after the procedure. It is worth noting that fewer patients benefited from CPN in 3 days compared with the number of patients who benefited in 1 week. This may be because, during the procedure, bupivacaine was used to bring relief from the pain originating from the injection, but its effect lasted only for about 24 hours while the neurolysis effect of alcohol may appear only in about 1 week. Further, the inability to completely control the pain in all patients as well as reduction in pain relief over time was observed in several studies.[11–14] The reason why alcohol injection into the plexus did not completely eliminate pain may be explained by pathologic studies of the plexus following treatment. Alcohol injection resulted in only partial destruction, degeneration, and fibrosis of the nerve fibers and ganglia.[15] Therefore, EUS-CPN results in pain relief only for a certain period and is not permanent.[16] In our study, this period was about 3 months.

A new finding in our study was that the efficacy of EUS-CPN is related to the duration of pain and to the baseline pain score before the procedure. The patients suffering from pain for a longer duration may experience less efficacy of CPN and a shorter period of pain relief. The reason may be associated with tumor staging. Long-term pain secondary to pancreatic cancer may indicate a later stage tumor, with broad or deep invasion of the peripancreatic and retroperitoneal nerves. Patients with higher pain score seem to have better pain control in the short time after CPN, but the benefits will not last longer. We observed that the percentage of substantial improvement in patients with a high score was significantly higher than that of patients with a lower score. This result was unexpected and may be difficult to explain. The patients who suffered more severe pain may be more sensitive to the change in pain level and hence may indicate a greater decrease in the pain score. However, these benefits were temporal, because the higher score may indicate a later stage tumor as well. Therefore, the prognosis of those patients was expected.

The site of injection is also important and may affect the result directly. Our study showed that CGN was more efficient than CPN, which is similar to the observation in another study.[17,18] The result may be explained by the mechanism of neurolysis. In the CPN, ethanol causes the demyelination of nerve axons, blocking the nerve conduction by dispersion effect[19]; however, the block does not last for long, and axonal degeneration will start and be gradually restored in 2 weeks.[20] In the CGN, ethanol destroys the cyton of the neuron, blocking the conduction, and the effect will last longer. The neurolysis is harder to restore. Levy et al[21] found the tumor cells in the celiac ganglia of patients with pancreatic cancer by means of EUS-FNA and explained that the mechanism of nociception in patients with pancreatic cancer was related to perineural invasion of the pancreatic nerves by the tumor. Furthermore, visualization of the celiac ganglia with direct injection into the ganglia may be considered the best predictor of pain improvement after EUS-CPN.

Our study showed that EUS-CPN was associated with a very low risk of complications. Transient hypotension can be prevented by intravenous infusion of Ringer lactate, saline, or glucose solution to guarantee adequate fluid circulation.

EUS-CPN is a promising technique for pain management in patients with pancreatic malignancy. Although the efficacy of EUS-CPN has been established, there are still many controversies surrounding its use. Our study suggests that patients with pancreatic cancer who need advanced pain control should undergo EUS-CPN as soon as possible. Further, if the celiac ganglia are visible in the EUS image, it is better to perform CGN instead of CPN.

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