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ORIGINAL ARTICLE

Neurolytic celiac plexus block reduces occurrence and duration of terminal delirium in patients with pancreatic cancer

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Abstract
Purpose WHO's three step ladder sometimes cannot provide adequate pain relief for pancreatic cancer. Some patients develop terminal delirium (TD). The aim of this study was to test if the addition of a celiac plexus block (CPB) to pharmacotherapy could reduce the incidence of TD.
Methods Pancreatic cancer patients under the care of our palliative-care team were investigated with regard to the duration and occurrence of TD, pain scores [numerical rating score (NRS)] and daily opioid dose. Between August 2007 to September 2008, 17 patients received only pharmacotherapy (control group). Then, we modified our guideline for analgesia, performing CPB 7 days after the first intervention of our team. Between October 2008 to September 2009, 19 patients received CPB.
Results The opioid doses in CPB group were significantly lower both at 10 days after the first intervention (3 days after CPB) (27 ± 11 vs. 66 ± 82 mg; $p = 0.029$) and 2 days before death (37 ± 25 vs. 124 ± 117 mg; $p = 0.009$). NRS in the CPB group were significantly lower both at 10 days after the first intervention (0 [0–2] vs. 3 [2–5], $p < 0.0001$) and 2 days before death (1 [0–2] vs. 3 [1–4.5], $p = 0.018$). The occurrence and duration of TD in CPB group were both reduced (42 vs. 94 %, $p = 0.019$; and 1.8 ± 2.9 vs. 10.4 ± 7.5 days, $p = 0.0003$).
Conclusion The duration and occurrence of TD and the pain severity were significantly less in pancreatic cancer patients who underwent neurolytic CPB.

Keywords Pancreatic cancer · Terminal delirium · Celiac plexus block

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Introduction

Since pancreatic cancer is an aggressive tumor, prognosis is poor and some patients are in severe pain at time of diagnosis [1–3]. Thus, pain relief and maintenance of quality of life are challenges even in the early stages of the disease. However, the recommended systemic analgesics according to the World Health Organization (WHO) analgesic ladder often do not provide adequate pain relief in patients with pancreatic cancer [2]. Moreover, irreversible delirium is often observed in patients with pancreatic cancer. Because the etiology of delirium in advanced cancer patients is usually multifactorial (cancer byproducts, intracranial disease, electrolyte imbalance, paraneoplastic syndrome, endocrine disorder, use of analgesics and psychoactive agents, dehydration, hypoxemia, infection and organ failure), use of opioids is one of the most frequent etiologies [4]. Some researchers consider the use of a neurolytic celiac plexus block (CPB) to be optimal for the management of refractory pain and a reduced usage of opioids [2, 3]. Thus, we have used computed tomography-guided CPB for the disease since October 2008.

We hypothesized that neurolytic CPB for patients with pancreatic cancer could reduce the incidence of terminal

delirium. The main aim of this study was to test our hypothesis that the addition of neurolytic CPB to pharmacotherapy could reduce the incidence of terminal delirium.

Methods

The present study was conducted from August 2007 to September 2009 by analyzing terminal delirium in all consecutive pancreatic cancer patients of a bed unit who were referred to our palliative-care team in Aichi Medical University Hospital in order to manage upper abdominal pain and/or back pain. Treatment protocols used in the present study were based on institutional policy and clinical guidelines. In October 2008, treatment guidelines were modified by our palliative-care team as a result of the preliminary findings in the present study. The treatment guidelines for patients with pancreatic cancer are as follows: Patients who are referred to our palliative-care team will be candidates for CPB while receiving the recommended systemic analgesics according to the WHO analgesic ladder, although CPB is not indicated for patients with uncorrectable coagulopathy or allergy to local anesthetics or alcohol, or reluctant to undergo CPB. The present study was approved by the Ethics Committee of Aichi Medical University.

All patients treated by our palliative-care team between August 2007 and September 2009 were included in the present study, and patients with dementia, substance abuse, brain metastasis, or other psychiatric disorder were excluded. Seventeen patients who were treated with opioid pharmacological management according to the WHO analgesic ladder between August 2007 and September 2008 formed a retrospective control group. Clinical data for this group were collected retrospectively from their medical records. The treatments guidelines were modified in October 2008 as mentioned above. Between October 2008 and September 2009, 19 patients underwent a neurolytic CPB addition to the WHO analgesic ladder, and they formed a CPB group. Written informed consent from each patient in the CPB group was obtained. Two patients in the control group and one patient in the CPB group were excluded because of brain metastasis.

The patients underwent a CPB operation 7 days after the first intervention of our palliative-care team. The CPB operations were guided by computerized tomography (CT). A traditional posterior approach technique was used with patients placed prone [5]. After we estimated the appropriate vertebral level for insertion, a 140 mm, 23-gauge needle with a scale was then inserted at the level of the first lumbar vertebra, 4–6 cm away from the midline, below the twelfth rib. After infiltration of 1 % lidocaine 3 ml at the site of insertion, the needle was advanced toward the front of the vertebral body. Repeated CT scans were taken in order to direct the needle 0.5–1.0 cm in front of the vertebral body, near the aorta. After confirmation of the needle tip location and the spread of contrast medium (Omunipark®240, Daiichisankyo, Tokyo, Japan), 14 ml absolute alcohol (Ethanol 99.5 %, Maruishi Pharmaceutical, Osaka, Japan) was injected.

Patients in both groups had been treated with pharmacological therapy by opioids and adjuvants according to the WHO analgesic ladder, beginning with their first visit to our outpatient department. All patients in the two groups came 3 days later for drug titration. Some patients were discharged from hospital after adequate pain relief, but were admitted again to the hospital for end-of-life care based on the physician's judgment that they were unlikely to live for 2 months.

A numerical rating scale (NRS) for pain on ranging from 0 to 10 (0 = no pain, 10 = worst pain imaginable) and daily opioid dose (oral morphine equivalents [6]) were evaluated and recorded at days 1, 3 and 10 after the first intervention of our palliative-care team and 2 days before death. Furthermore, clinical features of delirium were evaluated by nurses three times per day using delirium observation screening (DOS), which was developed based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria [7–9]. The DOS scale contains 13 items that can be rated as being present or absent in less than 5 min. The highest possible total score is 13. Three or more points indicates delirium. After indication, delirium was diagnosed clinically using DSM-IV criteria by a psychiatric doctor (M. N.). Dementia, substance abuse, and other mental disorders that frequently present psychotic symptoms were excluded. Terminal delirium was defined as delirium during the final 3 weeks of life. The duration of terminal delirium from occurrence to death was recorded.

The data are expressed as mean ± standard deviation (SD) for parametric values or as median [interquartile range] for non-parametric values. Since NRS is discrete variables, the results of NRS were analyzed non-parametrically. Following the Kolmogorov–Smirnov test, intergroup comparisons in demographic characteristics of patients at first visit and survival days after the first visit were analyzed by using the unpaired t test or the Fisher's test. $p < 0.05$ was considered statistically significant.

Results

The two groups were comparable with respect to demographic data and survival days after the first intervention of our team (Table 1).

Table 1 Demographic characteristics of patients at first visit and survival days after the first intervention

	CPB group ($n = 19$)	Control group ($n = 17$)	p
Age (year)	69 ± 6	66 ± 7	0.1069
Sex (M/F)	9/10	8/9	1.0
Weight (kg)	52 ± 8	54 ± 8	0.2908
Karnofsky performance status score	72 ± 14	76 ± 14	0.3642
Survival days after first visit	63 ± 25	63 ± 39	0.9364

Values are mean ± SD or numerical

Table 2 Daily opioid dose and numerical rating scale (NRS)

	CPB group ($n = 19$)	Control group ($n = 17$)	p
Daily opioid dose[a] (mg)			
1 day after the first intervention	27 ± 11	32 ± 17	0.324
3 days after the first intervention	27 ± 11	34 ± 17	0.243
10 days after the first intervention	27 ± 11	66 ± 82	0.029
2 days before death	37 ± 25	124 ± 117*	0.009
NRS			
1 day after the first intervention	4 [3–5]	5 [3–6]	0.112
3 days after the first intervention	2 [2, 3]	3 [1.5–4.5]	0.442
10 days after the first intervention	0 [0–2]*	3 [2–5]*	<0.0001
2 days before death	1 [0–2]*	3 [1–4.5]*	0.018

Values are mean ± SD or median [interquartile range]

CPB celiac plexus block

p, inter-group comparison

* Intra-group comparison with 1 day after the first intervention ($p < 0.05$)

[a] Oral morphine equivalent

Mild transient hypotension was observed in 6 patients of the CPB group. The daily opioid doses equivalent to oral morphine significantly increased in the control group in order to control cancer pain (Table 2). In contrast, CPB significantly reduced NRS and prevented the daily opioid doses from increasing (Table 2). The daily opioid doses at 10 days after the intervention of our palliative-care team (3 days after CPB) and 2 days before death in the CPB group were significantly lower than those in the control group (10 days after the intervention, CPB, 27 ± 11 mg, vs. control, 66 ± 82 mg; $p = 0.029$: 2 days before death, CPB, 37 ± 25 mg, vs. control, 124 ± 117 mg; $p = 0.009$). NRS at 10 days after the intervention and at 2 days before death were significantly lower in the CPB group (10 days after the intervention, CPB, 0 [0–2], vs. control, 3 [2–5]; $p < 0.0001$: 2 days before death, CPB, 1 [0–2], vs. control, 3 [1–4.5]; $p = 0.018$) (Table 2). Moreover, the occurrence and duration of terminal delirium in the CPB group were significantly less than those of the control group, respectively (42 vs. 94 %, $p = 0.019$; and 1.8 ± 2.9 vs. 10.4 ± 7.5 days, $p = 0.0003$, respectively) (Table 3). There were no significant intragroup differences in daily opioid doses between the patients with delirium and those without delirium in both groups (CPB, with delirium, 36 ± 21 vs. without delirium, 39 ± 30: control, with delirium, 124 ± 121 vs. without delirium, 120). Despite haloperidol or droperidol, mild to moderate delirium continued till death. After haloperidol or droperidol failed, three patients in the control group needed sedation for delirium.

Discussion

The main findings of the present study are as follows: (1) the addition of CPB to the systemic analgesics according to the WHO analgesic ladder significantly decreased the incidence and the duration of terminal delirium and the daily opioid doses in patients with pancreatic cancer; (2) intragroup analysis revealed that over 40 % of patients who received CPB developed delirium and the remaining patients who received CPB did not; there was no difference in the daily opioid consumption at 2 days before the death among them.

There is a high incidence of delirium and cognitive disorders in terminal cancer patients [10–12]. Many patients with pancreatic cancer, especially, experience terminal delirium over a relatively long period of time as shown in the present study. Agitated delirium causes severe distress for both patients and their family members, and complete remission of delirium is difficult to achieve. Haloperidol or chlorpromazine is used as the first line pharmacological treatment, and if the first line treatment failed, benzodiazepine and barbiturate were used to achieve symptomatic relief [12, 13]. Since there is no internationally accepted standard for palliative sedation at the end of life, inappropriate use of sedation could cause unnecessary reduction in consciousness levels and could be interpreted as a kind of euthanasia [14, 15]. Thus, the prevention of agitated delirium is crucial in our clinical practice. As shown in the present study, CPB reduced the duration and occurrence of terminal delirium, which might have alleviated unnecessary distress for both patients and their family members and ethical dilemmas for medical staff.

Terminal delirium was observed in 42 % of patients who received CPB, though it was significantly lower than that in the control group in the present study. The etiology

Table 3 Terminal delirium characteristics

	CPB group ($n = 19$)		Control group ($n = 17$)		p
Terminal delirium	+	−	+	−	
Occurrence rate	8 (42 %)	11 (58 %)	16 (94 %)	1 (6 %)	0.019
Duration (day)	4.4 ± 3.2	0	11.9 ± 7.2	0	
	1.8 ± 2.9		10.4 ± 7.5		0.0003
2 days before death					
Daily opioid dose[a] (mg)	36 ± 21	39 ± 30	124 ± 121	120	
NRS	0.5 [0–1]	1 [1–3]	3 [1.25–4.75]	4	

Values are mean ± SD, median [interquartile range] or numerical (percent)

NRS numerical rating scale

p, inter-group comparison

[a] Oral morphine equivalent

of delirium in advanced cancer patients is usually multifactorial, and use of opioids is only one of them [4]. There were no significant intragroup differences in daily opioid doses between the patients with delirium and those without delirium in both groups in the present study. Therefore, we have to take other factors into consideration. The celiac plexus is the largest of the three great plexuses of the sympathetic nervous system (the cardiac, celiac and hypogastric plexuses). Sympathetic nerves control organ function. Several studies showed that the blockade to splanchnic nerves, including sympathetic nerves, affects endocrine-metabolic responses to invasive procedures [16, 17]. The greater and lesser splanchnic nerves form the celiac plexus. Thus, CPB might have influenced endocrine-metabolic activity in patients with pancreatic cancer, thereby affecting the incidence and the duration of terminal delirium.

Delirium is common in the last weeks of life in people with advanced cancer. Several studies have shown that delirium was observed at an average between 2 and 3 weeks before death [11, 12, 18] and have identified delirium as an important factor indicating a poor prognosis in advanced cancer [4, 18]. We thus defined terminal delirium in the present study as delirium during the final 3 weeks of life. We evaluated pain intensity and the consumption of opioids at 1, 3, and 10 days after the first visit (6, 4 days before and 3 days after CPB) and 2 days before death. Since we tried to show the immediate and later effects of CPB on pain relief, we selected these time points in the present study. In fact, CPB provided good pain relief and restrained the opioid consumption.

There is a major limitation to the present study. We compared an interventional group to a historic control group. Although a randomized controlled study would be preferable in order to draw more definitive conclusions, we have to provide our best care for these patients in clinical circumstances and thus we used historical data as the control.

In conclusion, the duration and occurrence of terminal delirium were significantly less in pancreatic cancer patients who underwent neurolytic CPB.

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