Journal of BUON **15:** 715-719, 2010

ORIGINAL ARTICLE

Should interventional pain management in patients with pancreatic cancer be guided by tumor localization?

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Summary

Purpose: *To investigate the impact of pancreatic cancer localization in relation to the response to different interventional pain management methods and determine the method most suitable for satisfactory pain control.*

Methods: *Interventional pain management was carried out by sympathetic block or spinal analgesia. Patients were allocated into 2 groups according to the tumor localization, namely group 1 (n=61; patients with pancreatic cancer confined to the head of pancreas), and group 2 (n=55; patients with pancreatic cancer confined to the body or tail of pancreas).*

Results: *Among the patients who had interventional pain management, sufficient analgesia was achieved by sympathetic block in 9 of the 14 (64.3%) of them in group 1 and only in 3 of the 11 (27.3%) patients in group 2. Spinal analgesia was used in 5 of the 14 (35.7%) patients who required interventional pain management in group 1 and in 8 of the 11 (72.7%) patients in group 2 (p>0.05).*

Conclusion: *Pain palliation could be achieved by sympathetic block in patients with cancer localized in the head of pancreas while patients with tumor localized in the body and tail experienced sufficient pain palliation by spinal analgesia rather than sympathetic block.*

Key words: pain management, pancreatic cancer, spinal analgesia, sympathetic block, tumor localization

Introduction

Cancer of the pancreas may be confined to the head, body or tail. Around 65% of pancreatic cancers are localized in the head, 20-30% are localized in the body-tail while the rest show combined localizations [1-3]. Early diagnosis is often difficult due to rather vague initial symptoms and therefore patients are usually diagnosed in advanced stages [4-6]. Severe pain refractory to opiates can occur, especially in advanced disease stages, creating need for interventional pain management.

The cause of pain in pancreatic cancer is usually related to invasion of the celiac plexus by the tumor, obstruction of the pancreatic duct and consequent distention, inflammation and ischemia [7-9]. In short, pain in pancreatic cancer seems to be multifactorial [10,11]. Therefore, different treatment modalities may be utilized in pancreatic cancer patients for pain management.

The analgesic ladder system devised by World Health Organisation (WHO) is fundamental for pain management in pancreatic cancer. It has been shown that sufficient analgesia can be achieved in the majority of patients by systemic analgesic therapy [12]. However, advanced-stages patients may require interventional pain management. Interventional pain management helps reduce the systemic side effects of oral opiates and thereby increase patient compliance to treatment and quality of life. The efficacy of sympathetic block in pancreatic cancer patients has been shown in numerous studies [13-15]. On the other hand, studies also exist which argue that the duration of action of sympathetic block is short and its effect is insufficient [16-19]. Spinal analgesia, on the other hand, helps reduce the side effects by decreasing the amount of oral opiate taken [12]. Spinal analgesia is more effective than sympathetic block in advanced-stage pancreatic cancer patients when the tumor has invaded and metastasized and when somatic and neuropathic pathways are involved [12,19,20]. Pancreatic cancer patients de-

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Received 10-11-2009; Accepted 05-12-2009

scribe different responses to different pain treatments. It has been argued that tumor localization may be responsible for the varied responses of analgesic treatments, though the exact causes of these differences are yet to be determined.

The objectives of the present study were to investigate the impact of tumor localization in relation with the response to interventional pain management methods observed in patients with pancreatic cancer and to determine the most suitable method for satisfactory pain management.

Methods

Following Ethics Board approval, patients diagnosed with pancreatic cancer and presented to the Tulay Aktas Oncology Hospital, Ege University and Algology Out-patient Clinic were included in the study. Patients and their relatives were informed about the study and written consent was obtained. During the initial assessment, patient demographic features and tumor stage were recorded and patients were followed-up death. During the follow-up period, the amount of analgesic drug consumption and interventional pain management methods, if and when necessary, were recorded. Tumor localization in the patients' medical charts was concealed by the person who enrolled the patients to ensure that researchers responsible for planning the pain management would be blind to the tumor localization. Pain management was carried out according to the WHO analgesic ladder. Once data were gathered, patients were divided into two groups: group 1: cancers localized in the head; and group 2: cancers localized in the body-tail. Comparisons were made between two groups.

Tumor localization was established using computed tomography (CT) or ultrasound. Disease staging was made according to the pTNM classification of International Union Against Cancer (UICC) [21].

Interventional pain management was given to patients when sufficient analgesia could not be achieved by systemic analgesic therapy (VAS >6) or when serious side effects were observed. The first step in interventional pain management was sympathetic blocks (celiac plexus block and/or splanchnic nerve block). Spinal anesthesia (spinal-epidural catheter/port catheter) was performed when there was no response to sympathetic block or if the clinical patient features were not suitable for sympathetic block.

All procedures were performed under sterile surgical conditions with fluoroscopic guidance. Patients were infused with 1000 ml lactated Ringer solution via a 18G intravenous catheter prior to the procedure. The vital parameters of the patients (heart rate, noninvasive blood pressure, and peripheral oxygen saturation) were monitored during the procedure. All patients had intravenous sedation with midazolam and fentanyl.

Celiac plexus block was performed by transaortic technique defined by Ischia et al. [22]. Forty ml of ethanol approx. 75% (30 ml of ethanol 96% +10 ml of lidocaine 10 mg/ml) were administered for neurolysis. A 22G, 15-cm-long needle was introduced from the left side of L_1. The needle was advanced, penetrating the posterior and then the anterior aortic walls, after a little blood was aspirated. The placement of the needle and spread of dye were confirmed by both antero-posterior (AP) and lateral x-ray views with the fluoroscope before injection.

Splanchnic nerve blockade was performed using Abram and Boas' technique [23]. Six ml of 6% phenol solution were administered bilaterally (a total of 12 ml). Twenty-two G spinal needles were introduced bilaterally at the 11th intercostal space, 6 cm from the midline and advanced to touch the anterolateral aspect of T_{11}. Again with AP and lateral views, the placement of the needles was confirmed using contrast dye under fluoroscopy.

Taking the clinical features of the patients into consideration, spinal analgesia was achieved by placing a simple tunneled epidural catheter, epidural port catheter or spinal port catheter. Catheters used for spinal analgesia were placed under fluoroscope guidance with patients laying in prone position. Epidural catheterization was performed at the levels of T_{12}-L_3 while spinal catheterization was made at the levels of L_2-S_1. The localization of the tip of the catheter was confirmed by radio-opaque dye. In patients who had simple tunneled epidural catheter placed, the subcutaneous tunnel and the epidural catheter came out from the skin 15-20 cm away from the midline and fixed to the skin with a suture. When spinal-epidural port catheter was placed, the subcutaneous tunnel was extended towards the midclavicular line, the reservoir was placed in a subcutaneous pocket made at the level of the inferior ribs and sutured to the underlying fascia.

Statistical analyses

Descriptive Tables and statistical analyses were made with SPSS 13 statistical program. Age and sex distribution of the patients between the groups were calculated by the Student's t-test and chi-square test, respectively. Stage of the disease at the time of the diagnosis, WHO analgesic consumption, pain management and interventional pain management were analysed with Pearson chi-square test. $p<0.05$ was considered as statistically significant.

Results

A total of 116 patients (61 in group 1 and 55 in group 2) were assessed. No statistically significant difference was observed between the two groups concerning demographic features ($p>0.05$). Baseline characteristics of the patients are summarized in Table 1. Disease stage at the time of diagnosis was considerably more advanced in group 2 patients compared to group 1 patients ($p<0.05$). Similarly, analgesic requirements of patients at the time of diagnosis were statistically higher in group 2 than in group 1 ($p<0.05$; Table 1).

Sufficient analgesia was achieved by systemic analgesic therapy in 91 of the 116 patients (78.4%), whereas a total of 25 patients (14/23% in group 1 and 11/20% in group 2), had interventional pain management (Figure 1). No statistically significant difference was noticed concerning the need for interventional pain management between groups ($p>0.05$).

In 9 of the 14 group 1 patients (64.3%) who needed interventional pain management, sympathetic block was sufficient, whereas spinal analgesia was required in 5 patients (35.7%). Sympathetic block managed to alleviate pain in 3 of the 11 patients (27.3%) in group 2 who had interventional pain management, while 8 patients (72.7%) needed spinal analgesia (Figure 2). Though there were clinically significant differences between groups, these differences were not statistically significant ($p>0.05$). Power analyses showed that, in 80% confidence interval and at a significance level of 0.05, at least 33 patients who needed interventional pain management were required in each group for a statistically significant result.

Table 1. Patient baseline characteristics

Characteristics	*Group 1 (n=61)*	*Group 2 (n=55)*
Age, years (mean±SD)	60.80±9.9	58.64±11.31
Gender, n (%)		
Male	40 (65.6)	35 (63.6)
Female	21 (34.4)	20 (36.4)
Tumor stage, n (%) *		
2	4 (6.6)	0
3	24 (39.3)	10 (18.2)
4	33 (54.1)	45 (73.8)
Analgesic ladder (WHO), n (%) *		
None	13 (21.3)	1 (1.8)
1. step	15 (24.6)	2 (3.6)
2. step	23 (37.7)	22 (40.0)
3. step	10 (16.4)	30 (54.6)

* $p<0.05$

Discussion

The results of the present study showed that sufficient analgesia could be achieved by systemic analgesic therapy in 78.4% of the patients with pancreatic cancer, while 21.6% of the patients were in need of interventional pain management, indicating that tumor localization was not an important factor for interventional pain management. However, tumor localization may have a role in choosing the method for interventional pain management. It was observed that sympathetic block was considerably more effective in patients with cancer of the head. On the other hand, sympathetic block did not yield sufficient pain palliation and, hence, there was a greater need for spinal analgesia in group 2.

Many factors can cause pancreatic cancer pain. Pain has been attributed to the obstruction of a vessel or a duct, or viscera by tumor infiltration, capsule distention or necrosis, inflammation and ulcer [24]. Moreover, neuropathic and somatic pathways –as opposed to visceral mechanisms– were also implicated in pain by many researchers [13]. Since pain may be induced by many different mechanisms, concurrent use of different treatment modalities may be required in pancreatic cancer patients. Therefore, in these patients, systemic analgesic therapy is fundamental in pain management

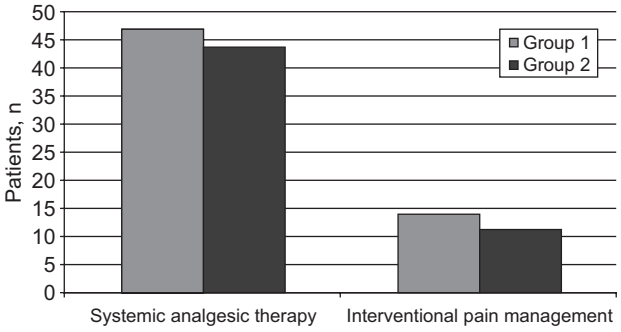

Figure 1. Pain management in different tumor localization of pancreatic cancer.

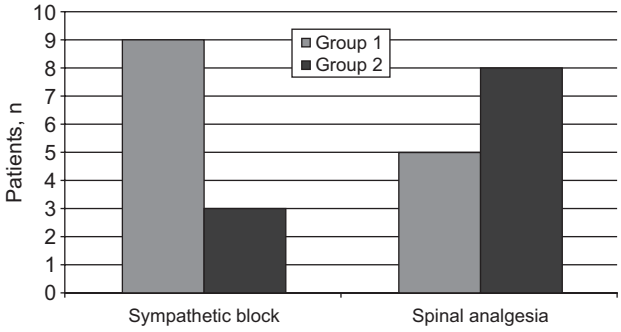

Figure 2. Interventional pain management in different tumor localization of pancreatic cancer.

from the time of diagnosis and onwards. In the present study, all our patients were given systemic analgesics at the time of diagnosis, in accordance with the WHO analgesic ladder. In agreement with the literature, sufficient analgesia was achieved with analgesics in 91 of the 116 patients (78.4%) [12].

Numerous studies report that sustained analgesia in patients with pancreatic cancer can be achieved by sympathetic block [13-15]. Therefore, we preferred sympathetic blocks first during interventional pain management because there is a great reduction in the need for repeated analgesics use in patients with pain relieved by sympathetic blocks. However, sympathetic blocks are not always effective in pain relief since pain is induced by different mechanisms in pancreatic cancer patients; insufficient or short-term analgesic effect has been reported in numerous studies [16-19]. Hence, it has been recommended that pain relief with analgesics be given to these patients before embarking on sympathetic block and that sympathetic block be performed if there is no response to analgesics [13]. In the present study we did not decide the timing of interventional pain management beforehand and gave analgesic treatment to each patient first. We performed sympathetic block when there was no adequate pain relief with analgesic treatment (VAS >6) or when serious side effects of the drugs were observed. Stefaniak et al. [25] compared the efficacy of neurolytic celiac plexus block with videothoracic splanchnicectomy in patients with inoperable pancreatic cancer and reported that both methods alleviated pain and improved the quality of life and concluded that celiac plexus block was a better option since it was a relatively less invasive method. As is the case in our routine clinical practice, amongst other sympathetic blocks, we preferred celiac plexus block. We performed splanchnic nerve block only when there was inadequate or short-lasting response to celiac plexus block. As a result, alleviation in pain intensity after sympathetic block in group 1 exceeded that in group 2. Furthermore, the need for repeated sympathetic blocks was less in group 1. Pain palliation with sympathetic blocks was not adequate in group 2 patients and they required spinal analgesia more than group 1. Sympathetic blocks were reported to be much more effective in pancreatic tumors localized in the head [13,26] and our findings are in agreement with these studies. Ozyalcin et al. [14] compared the celiac plexus block and splanchnic nerve block in patients with pancreatic cancer in the body-tail of the pancreas and they determined that splanchnic nerve block was more effective in such patients.

Another interventional pain management method used in pancreatic caner patients is spinal analgesia. The efficacy of spinal analgesia in pancreatic cancer has been established [20,27]. In the present study, we opted for spinal analgesia when adequate pain relief was not achieved by sympathetic block or when the patient's clinical features were not suitable for sympathetic block. The most common symptom in pancreatic cancer is visceral pain, observed in more than half of the patients. However, both visceral and somatic pain may be experienced by the patient, even in early stages [28,29]. When pain is not of visceral origin only, spinal analgesia is far more effective than sympathetic blocks. In our study, patients in group 2 benefited from sympathetic blocks less than those in group 1 and required spinal analgesia. This lower effectiveness of sympathetic block could be attributed to the more advanced tumor stage in group 2 patients at the time of diagnosis. Another explanation could be that the neurolytic agent is ineffectively distributed to the celiac plexus as a result of invasion of the neighboring structures by the tumor in early stages or pain is not only of visceral origin but also of somatic and neuropathic origins. Possible disadvantages of the spinal analgesia should also be considered. Disadvantages of this method in comparison to sympathetic blocks include necessity to use repeated analgesic agents for pain relief, catheter-related problems (malposition, infection, etc) and tolerance to the agents used [30]. Therefore, decision to perform sympathetic block or spinal analgesia should be made on an individual basis, especially in patients with tumor localized to the body-tail, and unnecessary interventions should be avoided.

Published studies that divided patients with pancreatic cancer according to the localization of the tumor have investigated either the prognosis [31] or the efficacy of the sympathetic blocks [13,14]. In the present study, treatment was given to all patients at the time of first diagnosis, using the same principles and without setting forth a prerequisite and knowing the tumor localization. Medical and interventional pain management methods were recorded, patients were divided into 2 groups during evaluation and differences were compared. Therefore, it was possible to eliminate bias in planning and ensure blindness in choosing the treatment.

Limitations of the present study include insufficient number of patients in each group who had interventional pain management, leading to inability for detection of statistically significant differences according to power analysis, and not assessing the quality of life.

In conclusion, the results of this study suggested that tumor localization is an important factor responsible for different responses to interventional pain management observed in pancreatic cancer patients. The results also imply that sympathetic blocks may be more advantageous in patients with cancer localized in the

head, whereas each patient with cancer of the body-tail should be assessed on an individual basis for interventional pain management, and spinal analgesia may be the first choice when necessary. We believe that our results would be a useful guide in clinical practice when choosing the most suitable pain management modality. No doubt, further studies are needed to enable a deeper look at the debilitating problem of pancreatic cancer pain and its management.

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