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Intrathecal Catheter Insertion and Analgesia is a Safe and Effective Method of Pain Control in Patients with Advanced and Intractable Cancer Pain

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Abstract

Introduction: Pain affects the quality of life in cancer patients. The World Health Organization established a simple three-step "ladder" approach in 1986, beginning with nonopioid drugs and progressing to stronger opioids as necessary. The implementation of this guideline enables analgesia to be achieved in 75% to 90% of patients. The remaining patients suffer from intractable pain requiring intrathecal analgesia. Advances in intrathecal analgesia and intrathecal drug delivery systems have allowed for a range of medications to be used in the control of pain in the remaining 20% of patients with intractable cancer pain. This technique allows for reduced medication doses that can decrease the side effects typically associated with oral or parenteral drug delivery. We aim to analyse the pain intensity before and after intrathecal analgesia and review the complications associated with the implantation and the care of the intrathecal device.

Materials and Methods: We retrospectively analysed medical records of all cancer patients whose pain were managed by intrathecal catheter implants in our centre from February 2005 to December 2014. The pain intensity was reviewed at the time prior to administration of intrathecal analgesia and at physician review prior to hospital discharge or death. Complications related to intrathecal analgesia were reviewed from the patients' medical records.

Results: We analysed the data obtained from 44 patients. 86.4% had metastatic cancer. Pain intensity was reduced significantly at the time of discharge from hospital ($P<0.001$). Opioids side effects were reduced after intrathecal treatment. The main catheter-related complications were catheter displacement and infection.

Conclusion: Intrathecal catheter insertion and analgesia is a safe and effective method of pain control in patients with intractable cancer pain.

Keywords: Intrathecal opioids; Intrathecal analgesia; Refractory cancer pain; Pain management

Introduction

Cancer pain management is increasingly becoming an important aspect of chronic pain and palliative care management as it is imperative that we provide comfort and care in these groups of patients [1]. For a segment of the cancer pain population, pain control remains inadequate despite full compliance with the WHO analgesic guidelines including use of co-analgesics [2]. Even amongst those whose cancer-related pain syndromes that can be controlled by systemically administered opioids, some patients still experience considerable side effects. The failure to obtain acceptable pain or symptom relief prompted the inclusion of a fourth step to the WHO analgesic ladder, which includes advanced interventional approaches [3]. Intrathecal (IT) analgesia is one option in the management of intractable cancer pain and in patients who cannot tolerate drug therapy [4]. However, despite anecdotal knowledge of the benefits of intrathecal analgesia in controlling cancer pain, there is still limited data in the literature on its benefits and risks. Due to the localised effect of intrathecal therapy, systemic side effects of morphine are largely reduced and there is localized analgesic effect at the site of action [4]. We performed a previous preliminary audit of the use of intrathecal analgesia for 29 patients with intractable cancer pain in Singapore General Hospital from February 2005 to August 2008 [5]. Since then, newer techniques for catheter insertion and new catheter designs were introduced which improved patient acceptance and this led to more widespread use of intrathecal techniques in cancer pain [6]. The number of cancer pain patients we see in our centre has also increased over the years and we hope to analyse the importance and use of intrathecal drug delivery in relieving pain compared to other modalities. This study aims to further extend the audit by increasing the sample size with the increased use of intrathecal catheters in patients with refractory pain, and add on to the results and conclusions from our previous study. This is important because with advancements in cancer treatments patients are living longer and cancer pain is one of the main symptoms affecting their quality of life [7]. We also want to look at the side effect profile to help us stratify patients in whom intrathecal analgesia would be beneficial, from patients in whom the risks would outweigh the benefits.

We hypothesize that the insertion of the intrathecal catheter improves the intractable pain of the cancer patients and improves their quality of life. We retrospectively analysed the pain intensity before and

after it drug delivery and evaluated the complications associated with the use of the IT device.

Materials and Methods

Institutional Review Board approval was obtained (Singhealth CIRB 2015/2533/D) prior to the start of the study, which waived the requirement of individual informed consent. Retrospective data was collected and analysed from the medical records of all cancer patients aged 21 and older whose pain were treated with IT analgesia at Singapore General Hospital Pain Management Centre between February 2005 and December 2014. The variables documented were: mean pain intensity was recorded using the Numeric Rating Scale (NRS) ("0" being "no pain" and "10" being "the worst possible pain") prior to IT catheter insertion (T_0) and at physician review prior to hospital discharge or death (T_d); mean daily systemic opioid consumption at T_0 and T_d, which was converted to the oral morphine equivalent dosage; and the mean daily dose of IT local anaesthetic and opioid doses in equianalgesic morphine equivalents. The presence of opioid-related side effects of opioids before and after IT drug delivery and device-related complications were also documented and compared.

Statistical analysis

Continuous data were presented as means with standard deviation (SD). We used the paired Wilcoxon signed rank test to compare pain intensity scores at T_0 and T_d and paired-sample Student's t-test to compare the mean IT opioid and local anaesthetic doses. The incidence of opioid-related side effects was analysed using the McNemar Test. All P values were two-sided, and P values <0.05 were considered statistically significant. Data were analysed by SPSS version 21.0 (SPSS Inc, Chicago, IL)

Results

We retrospectively analysed data from 44 patients (29 from the preliminary study and 15 additional patients recorded from January 2009 - December 2014) with intractable cancer pain managed by drugs administered via an IT catheter. Patient demographics are presented in Table 1.

The mean duration from T_0 to T_d was 2.4 months 59.1% of patients had the IT catheter (PORT-A-CATH® Intrathecal Implantable system, Deltec Inc, USA) inserted at the lumbar vertebral level. 1 patient received a cervical intrathecal catheter for pain relief from metastatic thyroid cancer. The choice of the catheter entry site was dependent on the location of the cancer and cancer-related pain – cervical catheters were reserved for head and neck cancers with refractory pain in the upper cervical dermatomes C1-C5; thoracic catheters were preferred for breast, lung and mediastinal tumours with referred cancer pain to the intercostal regions and thoracic dermatomes. As the use of hydrophilic intrathecal opioids like morphine permitted a higher cephalad spread [8], lumbar catheters were generally inserted for abdominal tumours such as oesophageal, pancreatic, gastric and colorectal cancers to achieve upper thoracic and lumbar analgesia. 39 patients received a combination of IT morphine and bupivacaine. Patient Controlled Intrathecal Analgesia (PCIA) was used in 20 patients, with an ambulatory patient-controlled analgesia infusion pump (CADD-Legacy® Model 6300, Smiths Medical, UK). This enabled patient autonomy over their pain control and allowed breakthrough pain to be expeditiously treated by self-administration of predetermined IT bolus dose as and when necessary.

No. of patients	44
Age (y)	51.8 ± 14.5
Gender: M/F	24/20
Primary Tumour	
Intra-abdominal	22 (50%)
Gynaecological	2 (4.50%)
Bone/muscle/breast	11 (25%)
Endocrine including thyroid	1 (2.30%)
Head and neck excluding thyroid	1 (2.30%)
Lung	4 (9.10%)
Unknown	3 (6.80%)
Metastasis	
Yes	38 (86.40%)
No	6 (13.60%)
Indications for intrathecal analgesia	
Intolerable side effects from opioids	4 (9.10%)
Uncontrolled pain	25 (56.80%)
Both	8 (18.20%)
Multidrug therapy	1 (22.70%)
Unknown	6 (13.60%)
Catheter entry site	
Cervical	1 (2.30%)
Thoracic	8 (18.20%)
Upper Lumbar	19 (43.20%)
Lower Lumbar	7 (15.90%)
No data	6 (13.60%)

Table 1: Patient demographics.

The average pain intensity recorded using the NRS was significantly reduced by 70% after administration of IT analgesia (7.4 ± 2.1 to 2.0 ± 1.7, P<0.001). Patients who received the combination mixture of IT morphine and IT bupivacaine 0.1% also reported significant reduction in pain scores (8.5 ± 4.2 to 21.0 ± 14.1, P<0.001). The doses of systemically administered opioids used after commencing IT analgesia was also significantly reduced from 530.8 ± 152.1 at T_0 to 35.6 ± 16.5 at T_d (P=0.002) (Table 2).

	T_0	T_d	P
NRS pain intensity	7.4 ± 2.1	2.0 ± 1.7	<0.001
IT bupivacaine dose (mg/day)	8.5 ± 4.2	21.0 ± 14.1	<0.001
IT morphine dose (mg/day)	4.5 ± 4.8	9.6 ± 15.6	0.09
Systemically administered opioids in oral morphine equivalents (mg/day)	530.8 ± 152.1	35.6 ± 16.5	0.002
IT: intrathecal, NRS: Numeric Rating Scale; Values are expressed as mean ± SD			

Table 2: Difference in Pain Intensity and Drug Dosages Administered Before and After Intrathecal Analgesia.

The incidence of opioid-related side effects was reduced in patients with IT analgesia, although the total reduction in opioid side effects was not statistically significant (20 (45.5%) to 16 (36.4%), P=0.7). 5 (11.4%) patients who received IT analgesia was found to be drowsy compared to 12 (27.3%) with systemic opioids. These patients who were drowsy were all end-stage cancer patients and died during their hospital stay.

Side effects	T_0	T_d
Somnolence	12 (27.3%)	5 (11.4%)
Nausea and vomiting	2 (4.5%)	2 (4.5%)
Constipation	2 (4.5%)	0
Weakness	0	5 (11.4%)
>1 complication	4 (9.1%)	4 (9.1%)
Total	20 (45.5%)	16 (36.4%)
Data is presented as number of patients with percentages in parentheses		

Table 3: Opioid-related Side effects.

Complications	n	%
Short-term complications		
Yes	8	18.2
High Pressure	5	11.4
Catheter displacement	3	6.8
No	36	81.8
Long-term complications		
Yes	4	9.1
Infection	2	4.5
No	40	90.9
Data is presented as number of patient and percentage		

Table 4: Complications from intrathecal drug delivery system implantation.

There was no change in the number of patients who presented with nausea and vomiting with systemic opioids compared to IT opioids. After administration of IT drugs, 5 patients experienced muscle weakness. These 5 patients all received the combination mixture of IT morphine and IT bupivacaine 0.1%. These adverse effects were short-lived and resolved before discharge from hospital (Table 3).

Catheter-related complications are divided into short and long term complications. Of the 44 patients who had IT catheter placement for pain control, 8 (18.2%) patients experienced short term complications. Of the 8, 5 patients experienced kinking of catheters triggering the high-pressure alarm after IT catheter insertion and 3 had catheter displacements. These complications were rectified by adjustment or repositioning of the IT catheter. 2 patients out of the 44 patients had infections related to the catheter and had to have their catheters removed and the patients were treated with systemic antibiotics. There were no reported long-term sequelae from the infections (Table 4).

Discussion

We present the treatment outcomes from the use of intrathecal catheters in the management of patients with refractory cancer pain in this article. We have shown that the use of intrathecal analgesia is a safe and effective method in the management of intractable cancer pain which leads to a reduction in the use of systemic opioids and hence their systemic side effects, better control of breakthrough pain with a lower dose of intrathecal opioids with a low incidence of short term and long term complications.

In 1999, the Joint Commission on Accreditation of Healthcare Organizations issued comprehensive standards of care for pain management. It stated, "No cancer patient should live or die with unrelieved pain" [8]. The World Health Organization established a simple three-step "ladder" approach in 1986, beginning with nonopioid drugs and progressing to stronger opioids as necessary [2]. Patients receiving adjuvant therapy and oral or transdermal opioids achieve adequate pain control in approximately 80% of cases. However, in 20% of patients, some form of alternative or invasive therapy is needed to control recalcitrant pain despite aggressive titration of these medications along the World Health Organization ladder [2,9].

Despite the anecdotal knowledge of the use of intrathecal analgesia in controlling intractable cancer pain, there is still limited data on the benefits and risks of intrathecal analgesia in current literature. We aimed to bridge this gap in knowledge with our study. We previously published a pilot study on the benefits of intrathecal analgesia in cancer patients [5]. We achieved a larger sample in this study and there was a consistent and significant reduction in pain score (72%) in patients who received IT analgesia. The total amount of opioid usage in patients who received IT analgesia was also significantly reduced. The results are again consistent with other studies that demonstrated the

benefits of IT analgesia in cancer patients. Advancements in implantable drug delivery systems (IDDSs) has led to increased acceptance and use of this treatment modality in managing cancer pain [10]. Patients with a limited life expectancy would benefit from a less invasive technique consisting of percutaneous port connected to an IT catheter. This system was used in most our patients with terminal stage cancer.

The choice of the catheter entry site was dependent on the location of the cancer and cancer-related pain–cervical catheters were reserved for head and neck cancers with refractory pain in the upper cervical dermatomes C1-C5; thoracic catheters were preferred for breast, lung and mediastinal tumours with referred cancer pain to the intercostal regions and thoracic dermatomes. As the use of hydrophilic intrathecal opioids like morphine permitted a higher cephalad spread [11], lumbar catheters were generally inserted for abdominal tumours such as oesophageal, pancreatic, gastric and colorectal cancers to achieve upper thoracic and lumbar analgesia.

Currently there are only three medications approved by the US Food and Drug Administration (FDA) for use via the intrathecal route, i.e., morphine, ziconotide, and baclofen [12]. Morphine remains the gold standard intrathecal opioid agonist, against which all other opioids are compared. Morphine target opioid receptors within the dorsal horn. It binds to receptors on the primary afferent neurons (presynaptic) and cells within the dorsal horn of the spinal cord (postsynaptic) to inhibit the release of neurotransmitters like substance P and calcitonin gene-related peptide and hyperpolarize postsynaptic neurons, respectively [13,14]. Intrathecal morphine, when compared with systemic morphine, results in lower side effects at lower doses while maintaining a concentrated analgesic effect. This is because morphine remains localized in the intrathecal space due to its hydrophilic nature compared to other lipophilic opioids and can spread to multiple levels of the spinal cord. There is reduced systemic spread of morphine and hence resulting in lower systemic side effects [15]. When combined with local anaesthetic, the dose of morphine administered into the intrathecal space is significantly reduced compared to systemic opioids [16]. This results in a significant reduction in drug toxicity and oral opioid requirements with improved pain control. Furthermore, with a baseline infusion of intrathecal morphine in cancer patients, a steady-state level of morphine is achieved and continuous pain relief is achieved. In contrast, patients who are on oral opioids alone experience fluctuations in the plasma level of opioids, with peak levels at the toxic range and the trough levels below the therapeutic index [17]. While waiting for their next dose of oral opioids, they may experience breakthrough pain. Therefore, significant improvement in pain can be achieved in cancer patients treated with IT morphine infusion systems.

90% of our patients received intrathecal infusions which are a combination of bupivacaine 0.1% and morphine. Previous animal and clinical studies have shown that intrathecal local anaesthetics such as bupivacaine potentiate the antinociceptive effects of opioids [18,19]. The opioid and local anaesthetic mixture has been shown to improve the quality of analgesia and reduce morphine usage. Side effects associated with low-dose bupivacaine such as hypotension and muscle weakness were observed but few. Muscle weakness was temporary and wore off with adjustment of infusion rates or local anaesthetic concentration and dose. With careful patient selection, combination mixtures of intrathecal infusions can achieve good pain control with minimal side effects. In addition, combination therapy reduced the development of opioid tolerance while proving synergistic analgesic effects [19]. While the mechanisms of synergism are not completely known, this has been postulated to be in part due to the modulation of Na+-, K+-electrochemical gradients and thus subsequent release of neurotransmitters in the spinal cord resulting in an enhancement of cholinergic transmission in the spinal nociceptive processing system [20].

The use of PCIA in our centre facilitates patient autonomy and control for incidental and breakthrough pain. Our pilot study first described the use of this technique in intractable cancer pain [5]. It continues to gain popularity in our centre. This technique provides better patient satisfaction as they are allowed to exercise control over their pain management. This may also in turn lead to reduction in opioid usage [21].

IT analgesia, being an invasive technique, is not without its side effects. The risk of infection after implant ranges from 0.8% to 9% [22] and this is an important risk as cancer patients who receive chemotherapy may be immunocompromised. Aseptic technique when inserting the catheter is paramount. Patients are also given prophylactic antibiotics to reduce the risk of infection. Short term complications such as high pressure in the catheter and catheter displacement can be rectified by vigilance and adjustment or repositioning of the catheter. Catheter dislodgement can be minimised by using specific methods of catheter placement. This includes a mid-to-upper lumbar dural entry level, a shallow-angle paramedian oblique insertion trajectory and meticulous catheter anchoring and tunnelling techniques. Postoperative device displacement and other device-related complications can be reduced by using systemic antibiotic prophylaxis, surgical wound closure techniques and paying close attention to pump pocket location [22]. As it is still an invasive technique, our centre reserves IT analgesia mainly for cancer patients with intractable pain not managed by the WHO cancer analgesia guidelines. Its use in non-cancer patients remains controversial and further studies could be designed to investigate the use of this technique in non-cancer chronic pain [23].

Conclusion

We described 44 cancer patients whose intractable pain was managed by intrathecal analgesia. IT analgesia provided significant improvement in pain control and decreased opioid side effects compared to systematically administered opioids. We have demonstrated that intrathecal catheter insertion and analgesia is a safe and effective method of pain control in patients with advanced and intractable cancer pain.

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