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Continuous Intrathecal Morphine Administration for Cancer Pain Management Using an Intrathecal Catheter Connected to a Subcutaneous Injection Port: A Retrospective Analysis of 22 Terminal Cancer Patients in Korean Population

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Background:

Intrathecal opioid administration has been used widely in patients suffering from severe cancer pain that is not managed with conventional modalities. However, the potential serious neurological complications from the procedure and the side effects of intrathecal opioids have made many clinicians reluctant to employ continuous intrathecal analgesia as a first-line therapeutic option despite its dramatic effect on intractable pain. We retrospectively investigated the efficacy, side effects, and complications of intrathecal morphine administration through intrathecal catheters connected to a subcutaneous injection port (ICSP) in 22 Korean terminal cancer patients with successful intrathecal morphine trials.

Methods:

Patient demographic data, the duration of intrathecal opioid administration, preoperative numerical pain rating scales (NRS) and doses of systemic opioids, side effects and complications related to intrathecal opioids and the procedure, and the numerical pain rating scales and doses of intrathecal and systemic opioids on the 1st, 3rd, 7th and 30th postoperative days were determined from medical records.

Results:

Intrathecal morphine administration for 46.0 ± 61.3 days significantly reduced NRS from baseline on all the postoperative days. A significant increase in intrathecal opioids with a nonsignificant decrease in systemic opioids was observed on the 7th and 30th postoperative days compared to the 1st postoperative day. The most common side effects of intrathecal opioids were nausea/vomiting (31.8%) and urinary retention (38.9%), which were managed with conservative therapies.

Conclusions:

Intrathecal morphine administration using ICSP provided immediate and beneficial effects on pain scores with tolerable side effects in terminal cancer patients. (Korean J Pain 2013; 26: 32-38)

Key Words:

cancer pain, complications, efficacy, intrathecal morphine, side effects.

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INTRODUCTION

Intrathecal therapy is often a final option after the failure of other treatment modalities. The invasiveness and high cost of intrathecal drug administration have limited its use despite considerable progress in the safety, efficacy, and side effects of intrathecal opioid administration techniques [1,2]. The reservation of intrathecal therapy as a last resort has been questioned since a multicenter study suggested that the early implementation of this treatment leads to improved outcomes [3]. A much wider application of intrathecal therapy for patients with cancer pain has been advocated recently [4]. However, there are only a few case reports regarding the use of intrathecal opioids in cancer pain in the literature published in Korea [5,6]. Therefore, we performed a retrospective analysis, examining pain intensity, doses of systemic opioids and intrathecal morphine, and the pharmacological side effects and technical complications of intrathecal morphine administration using intrathecal catheters connected to subcutaneous injection ports in Korean terminal cancer patients with successful intrathecal morphine trials.

MATERIALS AND METHODS

Twenty-two Korean terminal cancer patients, who received intrathecal morphine through an intrathecal catheter connected to an implantable subcutaneous injection port following intrathecal morphine trials that were successful in managing intractable cancer pain not responding to systemic opioids or other interventions, were included in this retrospective study, covering the period from June 2010 to September 2011.

Intrathecal catheterization with the implantation of a subcutaneous injection port (Celsite®, B. Braun, France) (Fig. 1A) was performed under aseptic conditions in the operating room. A 20-gauge intrathecal catheter was inserted through an 18-gauge Tuohy needle, using fluoroscopy, until the tip reached the intervertebral space between L1 and T12 (Fig. 1B). A subcutaneous injection port was placed within a subcutaneous pocket that was created caudal to the incision in the left or right lower abdominal quadrant (Fig. 1C). A bolus dose of 0.3 mg morphine (Morphine sulfate injection 5 mg/5 ml Hanlim®, Hanlim, Korea) was administered immediately after the placement

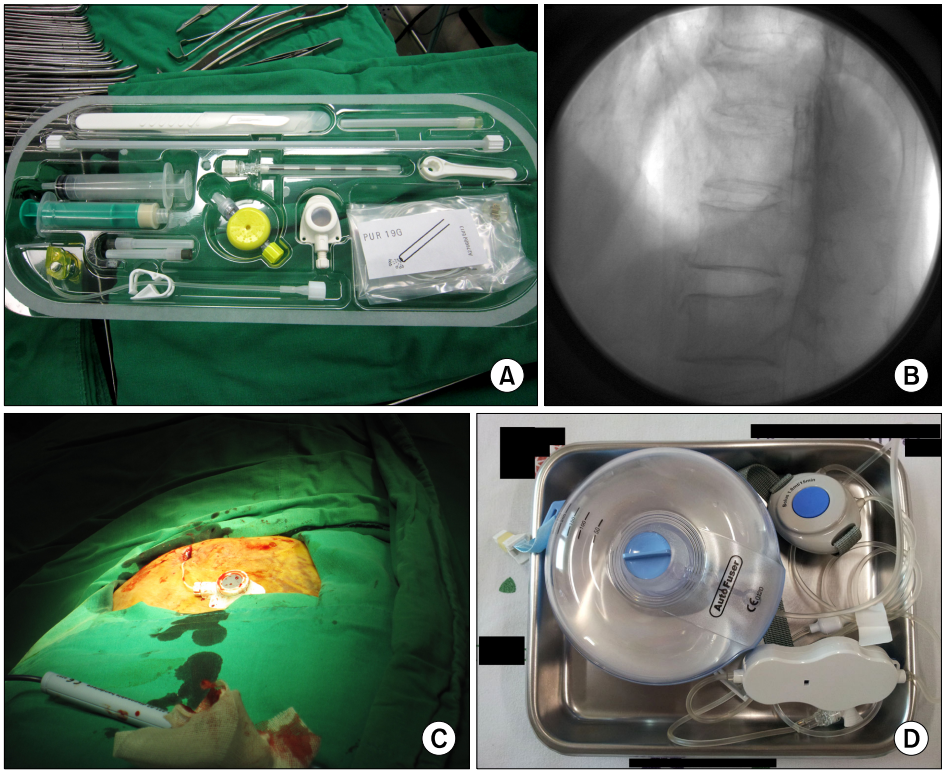

Fig. 1. Intrathecal catheter placement and implantation of a subcutaneous injection port. (A) A disposable intrathecal catheterization set and subcutaneous injection port. (B) Subarachnoid radiocontrast spread after the injection via intrathecal catheter. (C) A tunneled intrathecal catheter connected to the implantable subcutaneous injection port. (D) A patient-controlled analgesia device for continuous morphine infusion.

of an infusion device with a Huber bevel (Hubsite®, B. Braun, Germany) into the subcutaneous injection port. A patient-controlled analgesia device (Autofuser®, Ace Medical, Korea) containing 5-20 mg of morphine (1 mg/ml), with a total volume of 100 ml, was connected to the infusion device for continuous morphine infusion (Fig. 1D). The starting dose of morphine was low (continuous 0.6-3 mg/day morphine infusion with bolus 0.1-0.2 mg morphine and a 60-minute lock-out) to avoid the rapid conversion of systemic opioids to intrathecal opioids, which may unintentionally cause lower or higher expected opioid concentrations. The daily dose of intrathecal morphine was adjusted in the following days according to the pain intensity and the demanded and administered bolus doses during the last 24 hours.

Patient demographic data (e.g., sex, age, height and weight), type of cancer, follow-up period, technical data (e.g., insertion interspace, catheter tip location), preoperative numerical pain rating scales (0 indicates no pain and 10 indicates maximum pain) and non-pharmacological procedures to relieve the cancer pain, type and dose of systemic opioids, intrathecal opioid-induced side effects, and complications related to intrathecal catheterization and the subcutaneous injection port implantation were determined from the medical records. The numerical pain rating scales and systemic and intrathecal opioid consumption on postoperative days 1, 3, 7, and 30 were also assessed. The doses of the preoperative opioid pain medications were summarized as the oral morphine equivalent dose [7].

Table 1. Demographic Data, Type of Cancer and Follow-up Period

Gender (M/F)	13/9
Age (yr)	64.5 ± 11.9
Height (cm)	162.3 ± 11.2
Weight (kg)	54.6 ± 9.6
Type of cancer	
Lung	3 (13.6)
Upper gastrointestinal tract	3 (13.6)
Lower gastrointestinal tract	6 (27.2)
Hepatobiliary tract	3 (13.6)
Gynecological	4 (18.2)
Male genitourinary tract	1 (4.5)
Other	2 (9.1)
Follow-up period (day)	46.0 ± 61.3

Values are the means ± SD or number of patients (percentage).

Statistical analyses were performed using SPSS software (version 19.0, SPSS, Inc., USA). All the data are expressed as the mean ± SD or number of patients (percentage). All the follow-up data were compared with baseline measures using Student's t-test when assumptions of normality were met or the Wilcoxon signed-ranks test. A significant difference was acknowledged if the probability of a type 1 error was $< 5\%$ (i.e., $P < 0.05$).

RESULTS

The follow-up periods ranged from 6 to 276 days. Sixteen (72.7%) of the 22 patients who received intrathecal morphine through an intrathecal catheter connected to a subcutaneous injection port died 51.6 ± 69.1 days after the catheterization, and 6 patients (27.3%) remained alive (Table 1). Two patients had the intrathecal catheters and subcutaneous ports removed; 1 patient was transferred to another hospital, and another patient could not tolerate the pharmacological side effects. The majority of the intrathecal catheters were inserted at the L3-4 interspace (47.4%), and most of the catheter tips were located at the level of the T12 vertebral body (31.6%) (Table 2).

Fig. 2 presents the numerical pain rating scales at baseline and at each follow-up. The average numerical pain rating scales for the 22 patients decreased from 7.8 at baseline to 2.8 on postoperative day 1 ($P < 0.001$). A similar decrease in pain intensity was maintained for 30 days ($P < 0.001$).

Table 2. Interspace for Intrathecal Catheter Insertion and Catheter Tip Location

Interspace for intrathecal catheter insertion*	
L2-3	7 (36.8)
L3-4	9 (47.4)
L4-5	2 (10.5)
L5-S1	1 (5.3)
Vertebral body level of catheter tips*	
T10	3 (15.8)
T11	2 (10.5)
T12	6 (31.6)
L1	4 (21.1)
L2	3 (15.8)
L3	1 (5.3)

Values are the number of patients (percentage). *Derived from block sheets of the 19 patients in which technical data are available.

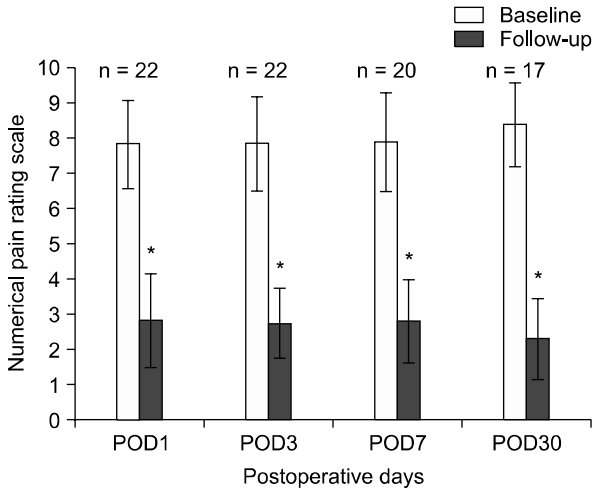

Fig. 2. Numerical pain rating scales at baseline and at the follow-up visits. The values are expressed as the means ± SD. Significant reductions in pain intensity on all the postoperative days compared to baseline were observed. *P < 0.001 compared to baseline using a paired t-test. POD: postoperative day.

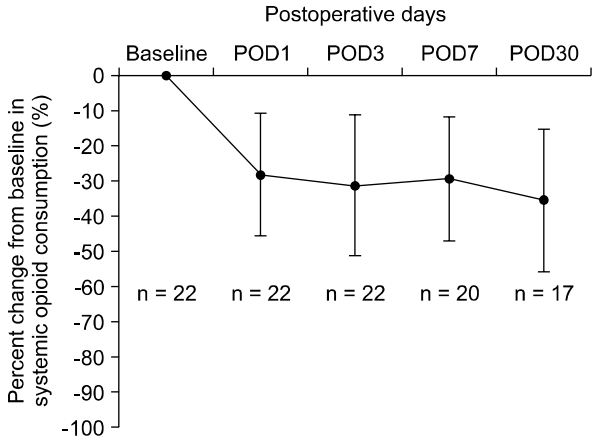

Fig. 3. Percent change from baseline in systemic opioid consumption. The values are expressed as the means ± SD. No significant changes in systemic opioid consumption were observed during the postoperative period. POD: postoperative day.

Preoperatively, one patient with liver metastasis from cholangiocellular carcinoma had undergone a neurolytic celiac plexus block, which failed to relieve the cancer pain, and all of the patients were receiving various types of systemic opioids (oral codeine, hydromorphone and oxycodone, intravenous and transdermal fentanyl, and intravenous morphine), which were 234.5 ± 200.6 mg of daily oral

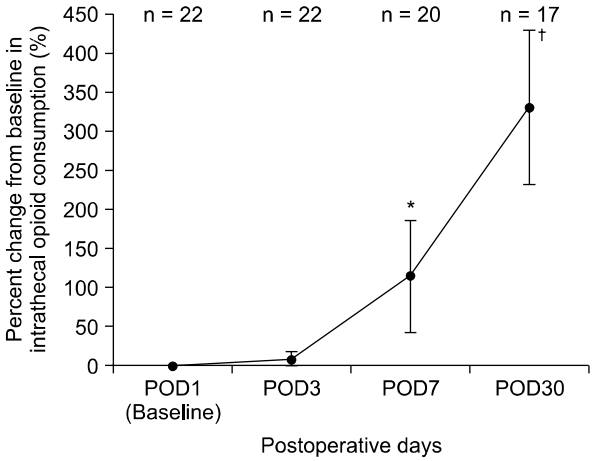

Fig. 4. Percent change from baseline in intrathecal opioid consumption. The values are expressed as the means ± SD. Significant increases in intrathecal opioid consumption were observed on postoperative days 7 and 30 compared to baseline. *P < 0.05 compared to baseline using the Wilcoxon signed-ranks test. †P < 0.01 compared to baseline using the Wilcoxon signed-ranks test. POD: postoperative day.

Table 3. Opioid-related Side Effects and Technical Complications

Pharmacological side effects	
Pruritus	1 (4.5)
Dizziness	2 (9.1)
Nausea and vomiting	7 (31.8)
Respiratory depression	1 (4.5)
Urinary retention	7 (38.9)*
Technical complications	
Postdural puncture headache due to cerebrospinal fluid leak	1 (4.5)

Values are the number of patients (percentage). *Derived from the 18 patients who did not undergo preoperative urinary catheterization.

equianalgesic doses of morphine. Three of the patients had completely withdrawn from systemic opioids at the last follow-up. Fig. 3 demonstrates the reduction in systemic opioid use as oral morphine equivalent doses in mg/day from baseline to each follow-up time. However, a significant change in systemic opioid administration compared to baseline was not observed.

In contrast, a significant increase in intrathecal opioids on postoperative days 7 and 30 compared to baseline was observed (Fig. 4). The mean doses at baseline and at the 3rd, 7th and 30th postoperative days were 1.6 ± 0.9 mg, 1.9 ± 1.2 mg, 4.4 ± 2.2 mg, and 8.6 ± 3.4 mg per day,

respectively. Two patients were receiving 24 mg and 33 mg intrathecal morphine per day at the 30-day follow-up.

Table 3 presents the opioid-related side effects and technical complications. Nausea and vomiting were the most frequently reported side effects of intrathecal morphine administration, and these effects subsided with conservative treatments within a few days. Urinary retention was managed by temporary urinary catheterization in 6 patients, although 1 patient was catheterized until death (Table 3). One patient (4.5%) experienced respiratory depression 7 hours after morphine infusion, which was readily reversed with intravenous naloxone. Two patients (9.1%) received an epidural blood patch for postdural puncture headache from a cerebrospinal fluid leak. Conservative treatments, including an epidural blood patch, did not relieve the headache in 1 patient who had received antituberculous drugs 1 month prior to the intrathecal therapy. This patient was subsequently diagnosed with tuberculous meningitis. No other complications of intrathecal drug delivery, including catheter kinking, catheter fracture/leakage, catheter migration, paresthesia on catheter threading, and pump erosion through the skin, were noted.

DISCUSSION

This retrospective study demonstrated a significant reduction in numerical pain rating scales with tolerable pharmacological side effects and technical complications during 30 days of intrathecal morphine administration through an intrathecal catheter connected to a subcutaneous injection port in terminal cancer patients with adequate pain relief in intrathecal opioid trials. Our results are consistent with previous studies that have demonstrated an improvement in clinical success and a reduction in pain scores using an intrathecal drug delivery system [3,8,9].

However, the consumption of systemic opioids decreased insignificantly despite a significant improvement in numerical pain rating scales and an increase in intrathecal opioid doses. These results are inconsistent with previous studies. The median daily systemic oral morphine equivalent doses fell from 250 mg to 50 mg in a previous randomized clinical trial [3]. However, the statistical significance was not reported, and the median intrathecal morphine dose was 2 mg/day in these patients during a 4-week evaluation [3]. An improvement in visual analogue scale pain scores from baseline to the 4-week time point was also observed [3]. Similarly, Rauck et al. [8] demonstrated a significant decrease in the median systemic opioid use and the average numeric analogue pain scores from baseline to monthly follow-up visits with an increase in median daily intrathecal doses (from 1.8 mg/day to 5.1 mg/day during 4 months of follow-up). These studies noted a 50% or greater reduction in systemic opioid use from baseline and a gradual increase in intrathecal opioid use, which differs from our results showing an insignificant decrease in systemic opioid use and a steep increase (over 300%) in intrathecal opioid use within 1 month. This discrepancy implies that the rapid progression of cancer in terminal cancer patients with a short life expectancy (nearly 73% of the patients died during 46 days of average follow-up time) aggravated the pain over time, which increased the absolute opioid dose requirement in this study.

There is a limit to the amount of morphine (maximum 16 mg/day) that can be delivered in a long-term intrathecal administration as excess administration may cause opioid-induced hyperalgesia [2]. However, this hyperalgesia rarely occurs [10]. Two patients in this study required more than 20 mg/day intrathecal morphine to maintain lower numerical pain rating scales. The development of tolerance likely produced the need to increase the dose over time to maintain a desired analgesic effect because high-dose intrathecal morphine did not produce hyperalgesia or allodynia in these patients.

The choice of external or totally implanted delivery systems is based on clinical considerations, such as life expectancy, physician experience, and costs [11]. Implantable drug delivery systems have been in general use in patients with chronic refractory cancer pain since 1991 [12]. However, the implantable drug delivery systems using intrathecal pumps in our country are very expensive, cannot be financed by the National Health Insurance, and are indicated only for a prognosis of more than 3 months. In addition, the small capacity of the intrathecal pump permits the delivery of only highly concentrated morphine, which may increase the risk of granuloma formation [13] when high doses of morphine are required to relieve pain. A simple percutaneous intrathecal catheter, which is a minimally invasive technique that can be performed at the bedside, can be used as a definitive method for intrathecal drug delivery when life expectancy is extremely short (i.e., days rather than weeks to months). The catheter is not

tunneled, which increases infection risk and mechanical failure and markedly reduces successful long-term use. In this study, 16 deceased patients survived for 51.6 ± 69.1 days after intrathecal catheter implantation, and 3 patients carried implanted intrathecal catheters for 37, 38, and 39 days until the last follow-up visit. These results demonstrate that the implantation of intrathecal catheters connected to subcutaneous injection ports was properly indicated for the patients in this study based on life expectancy, cost, and drug/dose requirements.

Side effects of intrathecal morphine therapy are common during the initiation phase of the treatment, but these effects generally resolve with standard medical management during the first 3 months [14]. The incidence of drug-related side effects with long-term intrathecal morphine therapy decreases with medical management and dose reduction as therapy continues [14]. Urinary retention following intrathecal morphine administration has an estimated incidence between 42% and 80% [15,16]. However, the incidence of urinary retention with long-term intrathecal morphine therapy is 3% [14]. The incidence of urinary retention, which was determined by excluding 4 patients with indwelling urinary catheters prior to intrathecal morphine administration, is not reliable in this study. The incidence of constipation was not determined because the majority of patients receiving systemic opioids in this study received a stool softener, a bowel stimulant, or laxatives prior to intrathecal opioid administration.

Based on the previous study reporting reduced hydrophilic compound concentration (43% of the T12 level concentration) surrounding the spinal cord at the T2 vertebral level when the compound was delivered over 72 hours into the lumbar subarachnoid space in patients with implanted drug pumps [17], the tip of the catheter was positioned relatively close to the segmental level of pain. Although most of the intrathecal catheter tips were located above the level of L1 (Table 2), where the spinal cord normally ends, the catheter passed easily with minimal resistance and no symptoms or signs of inadvertent entry of the catheter into the substance of the spinal cord were observed during its introduction into the subarachnoid space.

Our study had several limitations. First, only 22 patients were evaluated retrospectively. Five patients were lost or had died of cancer at the 30-day follow-up. An effective analysis of intrathecal opioid efficacy was not possible because the power at this small sample size is low. Moreover, disparity in the number of the patients at each follow-up day created unbalanced data. Second, long-term complications related to the intrathecal medications and technique, such as intrathecal infection or granuloma formation, could not be evaluated due to the relatively short follow-up period. Third, mild side effects, such as dizziness or pruritus, may have been underreported because the patients passively reported the incidence of pharmacological side effects in the retrospective setting of the present study. Fourth, the location of intrathecal catheter tips in the upper lumbar and lower thoracic vertebrae did not allow the use of additional lipophilic agents, which are more likely to enter the systemic circulation than hydrophilic agents, when morphine was not effective for pain management. Fifth, the preoperative pharmacological side effects of systemic opioids and pain mechanism (i.e., nociceptive or neuropathic) were unavailable. Therefore, it is not clear whether opioid-induced side effects are reduced following intrathecal therapy, and whether the effect of intrathecal therapy is dependent on pain mechanism.

In conclusion, intrathecal opioid administration using an intrathecal catheter connected to an implantable subcutaneous port in 22 terminal cancer patients provided a significant decrease in pain intensity with tolerable pharmacological side effects and a low incidence of intrathecal catheter-related complications. However, further prospective trials are warranted to confirm the long-term efficacy and safety of intrathecal opioid administration using this technique.

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