Retrospective Review

Intrathecal Analgesia via a Percutaneous Port With Patient-Controlled Intrathecal Analgesia for the Management of Movement-Evoked Breakthrough Cancer Pain of Refractory Lower Extremity Cancer Pain: A Retrospective Review

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Background: Intrathecal analgesia (ITA) is a valuable treatment option for refractory cancer-related pain. However, there is still no general consensus on the analgesic effect of movement-evoked breakthrough pain (MEBTP) in the ITA setting.

Objectives: This study aimed to conduct a retrospective observational study to examine the effect of ITA via percutaneous port (ITAPP) with patient-controlled ITA (PCIA) on analgesic efficacy, emphasizing MEBTP in patients with refractory lower extremity cancer pain.

Study Design: A retrospective chart review included all patients with refractory lower extremity cancer pain who received ITAPP at our hospital between January 2017 and December 2020.

Methods: Data on the Numeric Rating Scale scores of spontaneous resting pain intensity (SRPI) and MEBTP intensity (MEPI), opioid doses, and perceived time to onset were collected from medical records prior to ITAPP and at a one-month postimplant visit.

Results: A total of 16 patients were included in the study group. Mean SRPI decreased from 8.75 pre-ITAPP to 3.75 post-ITAPP ($P < 0.05$); mean MEPI fell from 8.83 pre-ITAPP to 4.25 post-ITAPP ($P < 0.05$); mean daily morphine equivalent dosing decreased from 360 mg/d to 48 mg/d ($P < 0.05$); and mean daily morphine equivalent dosing for MEBTP decreased from 87 mg/d to 6 mg/d ($P < 0.05$). Both total and breakthrough dosing of conventional opioid medications significantly decreased following the initiation of ITAPP with PCIA. The mean perceived time to onset with conventional MEBT medications was 38 minutes, and the mean perceived time to onset with PCIA was 8 minutes ($P < 0.05$).

Limitations: An effective analysis of IT opioid efficacy was not possible because the power of such a small sample size was low. Second, it is a retrospective study without long-term follow-ups.

Conclusions: In patients with refractory lower extremity cancer pain, ITAPP with PCIA was associated with improved pain control. Compared with conventional MEBTP regimens, appropriate ITAPP with PCIA provided superior analgesia and a much faster onset of action.

Key words: Movement-evoked breakthrough pain, patient-controlled intrathecal analgesia, lower extremity cancer pain, intrathecal analgesia via a percutaneous port

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Cancer-associated pain continues to present a significant problem, with a prevalence of up to 67% (1). There have been major advances in recognizing an appropriate treatment of cancer pain, largely related to the widespread adoption of the World Health Organization (WHO) "ladder" of pain management in the 1980s (2,3). However, even when the WHO approach is implemented appropriately and aggressively, 10% to 20% of patients do not attain acceptable pain or symptom control (4). In a prospective

study (5) that included 2,118 patients with cancer-related pain managed by the WHO analgesic ladder, 3% required intrathecal (IT) or epidural analgesia. It is generally regarded that IT analgesia (ITA) therapy offers a reliable, accurate, safe, and efficacious treatment for both cancer and non-cancer pain, as well as for end-of-life pain care (6-8).

Severe lower extremity pain is the main symptom of bone and soft tissue malignancies and bone metastatic tumors (9-11), while movement-evoked breakthrough pain (MEBTP) is widely recognized as the most difficult-to-treat clinical problem in these patients (12). BTP can be categorized into spontaneous BTP, end-of-dose failure, and incident pain, with MEBTP being a subtype (13,14). Due to fear of MEBTP, patients are afraid or unwilling to change body position, as this may bring a series of problems, including incision nonhealing, pressure sores, lung infection, urinary retention, and similar. More importantly, this may hinder patients' cooperation with routine examinations, as well as affect tumor evaluation and follow-up treatment. Although there have been some studies on ITA treatment of MEBTP, the reported conclusions are not consistent. Also, the issue of MEBTP on the lower limb has been poorly investigated in the ITA setting (15-17).

ITA via percutaneous port (ITAPP) is expected to take a shorter time to reach cost equivalence of IT morphine infusion therapy via an implanted port due to its relatively lower initial implantation costs, thus making it a better choice for advanced cancer patients with a short life expectancy (18,19). ITAPP is a percutaneous port attached to an external drug infusion pump that allows for continuous ITA for the management of spontaneous resting pain (SRP) and patient-controlled ITA (PCIA) for the management of MEBTP (16,20). We hypothesized that ITAPP with PCIA could not only increase the number of activities in patients and shorten the response time to deal with MEBTP, but it also improves overall pain relief and opioid-related adverse effects. The study aimed to conduct a retrospective observational study to verify our hypothesis and provide a useful reference for diagnosis and treatment of refractory lower extremity pain caused by a malignant bone tumor.

Study Design

We performed a retrospective chart review of data obtained from our Hospital Information System. We analyzed these medical records of patients with lower extremity cancer pain recently admitted to our hospital, all of whom used ITAPP. All patients were informed that their medical data might be used for research in the future before accepting ITAPP treatment, and they provided written informed consent. The study was approved by the ethics committee of our hospital on November 1, 2021 (ethic code IRBW-2021-011-01).

Methods

Patient Population

Between January 2017 and December 2020, ITAPP was performed for 70 patients with advanced cancer pain, 16 of whom were refractory lower extremity cancer pain patients implanted with an IT catheter connected to a percutaneous port for ITAPP. Four patients were excluded from the study for the following reasons: 2 patients died within one month of catheter implantation; one patient who suffered from mania could not use PCIA and follow the requirements; and one patient underwent notch split because of targeted therapy. Finally, 12 patients were included in the analyses. All procedures were performed by a single physician at our hospital, and under strict sterile operating room conditions with the patient under local anesthesia.

IT access was obtained in the lumbar region under the guidance of an x-ray. The IT catheter was implanted into the IT space, and the tip of the catheter was placed at the tenth thoracic vertebra (T10) level that was considered to best subserve the dermatomal distribution of the patient's lower extremity pain (data on pain location and catheter tip location are shown in Table 1). Then, a subcutaneous tunnel was built, and

Table 1. *NRS-11 pre- and post-ITT, onset time for MEBTP.*

	Preimplant Mean	Preimplant Standard Deviation	Postimplant Mean	Postimplant Standard Deviation	*P* value
SRPI	8.75	1.05	3.75	0.86	$P < 0.05$
MEPI	8.83	0.93	4.25	0.96	$P < 0.05$
Onset Time for MEBTP (min)	38.75	14.63	8	2.21	$P < 0.05$

Abbreviations: NRS-11 = numeric rating scale; ITT = intrathecal therapy; MEBTP = movement-evoked breakthrough pain; SRP I = spontaneous resting pain intensity; MEPI = movement-evoked pain intensity.

the catheter was connected to a subcutaneous port via the tunnel. Morphine and bupivacaine diluted with 0.9% sodium chloride solution to 250 mL were infused into the IT space through the subcutaneous port by an external drug infusion pump (21,22). IT morphine was initiated and titrated according to guidelines and clinical experience. Opioids given by systemic routes were gradually weaned off as needed.

Data Collection

A retrospective review was completed for all patients by examination of their electronic medical records. Patients' demographic data (e.g. gender, age), types of cancer, technical data (insertion interspace, catheter tip location), and complications related to ITAPP were obtained from the medical records. Numeric Rating Scale (NRS-11) scores and doses of opioids before and after ITAPP were also determined. The opioid used were compared using oral morphine equivalent dosing, which was derived from published recommendations for opioid equivalence. To attempt to evaluate the treatment effect of MEBTP, the use of immediate-release as-needed opioid medications was also listed and compared.

Outcome data were also taken from follow-up appointments. A follow-up visit at one month after port implantation was chosen as the most appropriate for postimplant data collection. This time period was selected to ensure that adequate dose titration of the IT medications was achieved and that postoperative incisional pain did not impact pain reporting. Medication data prior to and following port implantation were recorded for all patients. These data were obtained from the initial evaluation documentation and the pharmacy drug reconciliation data performed by our institution. Following port implantation, the pump was interrogated at each follow-up, and all pump data were recorded in the patients' chart.

Statistical Methods

Summary statistics (i.e., number, mean, standard deviation/error) were provided for age, gender, type of cancer, months since diagnosis, the reason for ITAPP, morphine oral equivalent dosing, patients using MEBTP medications, baseline NRS-11 score, months since diagnosis, and period of ITAPP. Frequency tables are provided for each categorical variable (i.e., oral morphine equivalent opioid dosing, IT morphine, and bupivacaine dosing [including PCIA], NRS-11 scores, onset time for MEBTP, and pump data). The primary outcome variable was the change in NRS-11 scores, including SRP intensity (SRPI) and movement-evoked breakthrough pain intensity (MEPI) before and one month after the ITAPP was commenced. The second outcome variable was the change in onset time for MEBTP. The third outcome variable was the increase of IT medication, including PCIA in MEBTP medication use. In addition, a comparison of morphine equivalent opioid dosing before and after ITAPP was performed. Changes in the use of oral analgesics were compared using the Wilcoxon signed-ranks test to evaluate the paired nonnormally distributed data, and a paired samples t test was used to evaluate data with normal distribution, including NRS-11 scores, onset time for MEBTP, and IT data. A $P < 0.05$ was considered to be statistically significant.

Results

Study Population

The final study population included 12 patients who received placement of an IT catheter for cancer pain. All patients could control BTP by using their external pump system. The follow-ups occurred from January 2017 to December 2020. The average follow-up period for data collection was 6 weeks. All demographic data are listed in Table 2. Osteosarcoma and fibrosarcoma were the most common types of cancer. Inadequate pain control was the most commonly cited reason for ITAPP. Other indications included intolerance of oral or transdermal opioids due to nausea, sedation, or refractory constipation.

Table 2. *Baseline patient characteristics*.

Age, y (mean, standard deviation)	48 ± 8	
Male Gender	7/12	
Type of Cancer	Osteosarcoma/ Fibrosarcoma	Bone Metastatic Tumor
Months Since Diagnosis (mean)	18 (mo)	
Reason for ITT	Poorly Controlled Pain	Intolerance
Pain Site	Leg	
Cather Tip Location	T10	
Morphine Non-IT Equivalent Dose, (mg/d)	360 ± 71 mg	
Patients Using MEBTP Opioids (mg/d)	87 ± 18 mg	
Baseline NRS-11 Pain Score	8 ± 0.3	
Mean Duration of ITT/mo	4 ± 0.8	

Abbreviations: IT = intrathecal; ITT = intrathecal therapy; MEBTP = movement-evoked breakthrough pain; NRS-11 = numeric rating scale.

All patients were using opioids for control of MEBTP. Mean NRS-11 scores were 8 ± 0.3 at the initial evaluation. The mean time for all patients until death was 3.5 ± 1.9 months. The data on patients' treatment, including age, diagnosis, pain site, catheter tip location, and their IT regimen at follow-up, are summarized and shown in Table 2.

Patient-Reported Pain Scores and Perceived Time to Onset

Between preimplant and postimplant, the distributions of the worst pain and the perceived time of onset are shown in Figs. 1 and 2. Mean SRPI decreased from 8.75 to 3.75; mean MEPI dropped from 8.83 to 4.25; and the observed difference was statistically significant ($P < 0.05$). The mean perceived time to onset with conventional MEBTP medications was 38.75 ± 14.63 minutes (range, 20-60 minutes), and the mean perceived time to onset with PCIA was 8 ± 2.21 minutes (range, 5-12 minutes). The t test pairs revealed a significantly faster onset of analgesia with PCIA ($P < 0.05$). Further details are shown in Table 1.

Non-IT Opioid Medication Use

All but one patient (who could not tolerate any oral pain medications due to nausea and vomiting) were on conventional opioid medications before commencing ITAPP. Before ITAPP, patients were taking a mean oral morphine equivalent to 360 mg/d (range: 90-800 mg/d). Following the catheter placement, the dose was lowered to 48 mg/d (range: 0-120 mg/d; $P < 0.05$). Before ITAPP, the patients were taking an average of 87 mg/d (range: 20-200 mg/d) of oral morphine equivalent short-acting (i.e., parenteral, immediate oral release, or oral transmucosal) medications for MEBTP (including oxycodone, hydrocodone, morphine, fentanyl, and hydromorphone). The MEBTP conventional medication use decreased to an average of 6 mg/d (range: 0-20 mg) following catheter placement ($P < 0.05$). Both total and breakthrough dosing of conventional opioid medications significantly decreased following the initiation of ITAPP with PCIA. These data are summarized in Table 3.

IT Pump Medications

All 12 patients included in this study received a

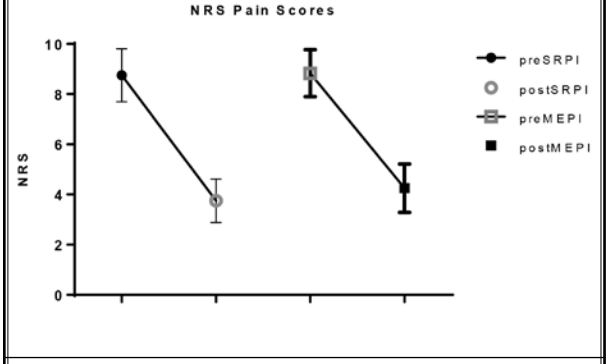

Fig. 1. *Numeric rating scale (NRS-11) scores of spontaneous resting pain intensity (SRPI) and movement-evoked breakthrough pain intensity (MEPI) before initiation of intrathecal analgesia via percutaneous port (ITAPP) and at one-month follow-up visit.*

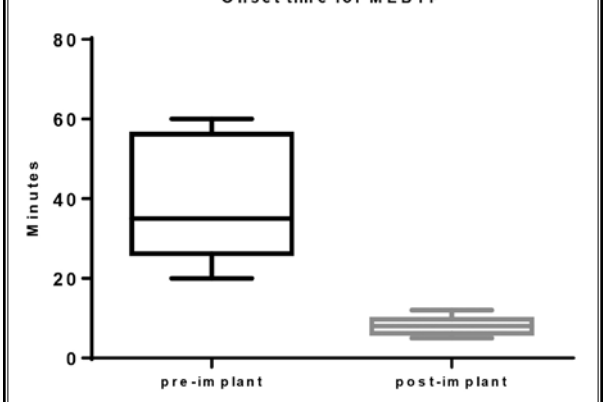

Fig. 2. *Perceived time to onset for movement-evoked breakthrough pain (MEBTP) prior to intrathecal analgesia via percutaneous port (ITAPP) and at one-month postimplant visit.*

Table 3. *Non-IT opioid medication use.*

	n	Preimplant Mean	Preimplant Median	Postimplant Mean	Postimplant Median	*P* value
Morphine Oral Equivalent Dose (mg/d)	12	360	322.5	48	40	$P < 0.05$
Breakthrough Morphine Oral Equivalent Dose (mg/d)	12	87	80	6	0	$P < 0.05$

Abbreviations: IT = intrathecal; n = number.

mixture of morphine and a local anesthetic (i.e., bupivacaine) as an effective part of their IT regimen. IT drug regimens are summarized in Table 4. All patients had the option to use PCIA for the management of their BTP. Patients had a significant increase in IT medication, including morphine and bupivacaine, on postoperative 30 days compared to baseline. The patients were taking an average of IT opioids from 1.85 mg to 27.87 mg, including PCIA morphine from 0.65 mg to 12.73 mg. The patients were taking an average of IT bupivacaine ranging from 0.94 mg to 14.54 mg, including PCIA bupivacaine from 0.33 mg to 6.48 mg. Patients used their PCIA device on average from 13.08 to 20.25 times a day. The average infusion speed of the pump increased from 0.11 to 0.99 mL/h. These data are summarized in Table 4.

Opioid-Related Side Effects and Technical Complications

Table 5 presents the opioid-related side effects and technical complications before and after IT treatment. Nausea and vomiting, constipation, and respiratory depression were the most frequently reported side effects of opioid administration. There were no significant changes in these effects compared to preoperative conditions. Two more patients had urinary retention compared to the preoperative state and were managed by temporary urinary catheterization. Two patients experienced a headache from a cerebrospinal fluid leak after a postarachnoid puncture, which was successfully relieved in both patients after conservative treatments. No other complications of IT drug delivery, including catheter kinking, catheter fracture/leakage, catheter migration, and paresthesia on catheter threading, were observed.

Discussion

In some patients with extremity osteosarcoma and bone metastases, MEBTP has been widely recognized as the most difficult to treat by conventional medical management, including oral or transmucosal opioids (23,24). IT morphine infusion therapy is an effective treatment option for refractory cancer pain; however, the general consensus on its effectiveness for MEBTP has not yet been reached (16,25). The purpose of this study was to investigate the efficacy of ITAPP with PCIA in the treatment of MEBTP of lower extremity tumors.

The implanted IT morphine pump is usually used for IT morphine infusion therapy and is suitable for long-term use. Yet, the high initial cost remains a major obstacle. Recently, ITAPP has become a widely used approach in some countries for its relatively lower cost (19). In the present study, we assessed the efficacy and safety of ITAPP.

Direct analgesic delivery to the neural axis offers immediate access to receptors, bypasses the blood-brain barrier, and minimizes systemic drug interactions. A commonly used mixture for the treatment of intractable pain consists of morphine and bupivacaine. Nevertheless, IT bupivacaine also provides better analgesia in patients with neuropathic pain than in patients with nociceptive pain (22) .

In their randomized controlled study, Bäckryd et al (25) evaluated an IT drug delivery system vs comprehensive medical management to treat advanced cancer pain, reporting significant improvement in SRPI. Nonetheless, MEBTP was not adequately controlled despite IT therapy (ITT). However, besides providing support that ITT is a valuable analgesic technique in SRPI, our results also revealed that MEBTP could be adequately controlled in patients with lower extremity osteosarcoma and bone metastases. Since the main purpose of this study was to explore MEBTP, we chose the lower extremity pain with the greatest impact of MEBTP. Our results revealed that MEPI significantly decreased after

Table 4. *IT pump medications.*

	n	Baseline Dose		Postoperative 30 days		*P* value
		Mean	SE	Mean	SE	
IT Opioid in Morphine Equivalent Dose (mg/d)	12	1.85	0.36	27.87	4.24	$P < 0.05$
IT Bupivacaine (mg/d)	12	0.94	0.17	14.54	1.55	$P < 0.05$
PCIA Opioid in Morphine Equivalent Dose (mg/d)	12	0.65	0.12	12.73	2.05	$P < 0.05$
PCIA Bupivacaine dose (mg)	12	0.33	0.06	6.48	0.60	$P < 0.05$
Infusion Speed (mL/h)	12	0.11	0.01	0.99	0.05	$P < 0.05$
Frequency of PCIA Use (times/d)	12	13.08	0.41	20.25	0.61	$P < 0.05$

Abbreviations: IT = intrathecal; n = number; SE = standard error; PCIA = patient-controlled intrathecal analgesia.

Table 5. *Opioid-related side effects and technical complications.*

Pharmacological Side Effects	Preimplant	Postimplant
Pruritus	1/12	2/12
Dizziness	1/12	1/12
Nausea and Vomiting	4/12	4/12
Respiratory Depression	2/12	2/12
Constipation	5/12	5/12
Urinary Retention	1/12	3/12
Technical Complications		
Postdural Puncture Headache due to Cerebrospinal Fluid Leak	0/12	2/12

one month of treatment. The proportions of the drugs in the study have been approved. Still, differences in concentration and dose and the rate of administration could be the most important reason for the diametrically different results of the 2 studies. In Bäckryd et al (25), their initial dose of IT morphine was adjusted according to pre-IT doses using an oral-to-IT ratio of 200:1. In the present study, we used the 300:1 ratio, which is in line with the Polyanalgesic Consensus Conference clinical recommendation (26). Our IT basal starting dose was less than or equal to their study. However, as they used a fully implantable pump with just 40 mL in volume, this limited the concentration and volume variation. The maximum capacity of the external pump we used was 250 mL, allowing us to configure the drug concentration flexibly. In their study, by a combination of morphine (0.2 mg/mL), bupivacaine (1 mg/mL) was IT infused. The usual starting rate was 0.5 mL/h with patient-controlled boluses of 0.2 mL available up to twice per hour as needed. In our study, the concentration of morphine (0.1-0.8 mg/mL), bupivacaine (1 mg/mL), and the dose of bolus were usually set to be consistent with the continuous infusion dose for one hour. The maximum speed was given to 2 mL/h, which means that the maximum single bolus dose was 2 mL. The lockout period was 10-15 minutes, so our single dose of bolus and the daily numbers of bolus were much higher than theirs, but the total dose we used was still within the safe range. At the same time, we customized the treatment for every patient and we always advised them to press the bolus button usually 5-10 minutes before their movement according to their pain intensity. PCIA offered the patient the ability to deliver a bolus of an opioid and local anesthetic to the neuraxis and produce rapid-onset analgesia.

Bäckryd et al (25) suggested that metastatic bone pain was precisely movement that evoked BTP. The pathophysiology of metastatic bone pain was a complicated matter, but on a basic level, it was reasonable to assume that weight-bearing and movement increase the nociceptive input into the spinal cord. Furthermore, this increase in nociceptive input could occur, especially if there were incipient or actual pathologic fractures or substantial cancer growth into adjacent neural structures. Thus, it seemed that advanced breast or lung cancer with concomitant neuropathic pain was a risk factor for intractable MEBTP despite an otherwise successful ITT.

All patients enrolled in our study were patients with lower limb tumors. More interestingly, in all the cancer pain patients we treated with ITA, lower extremity pain was more significantly relieved compared to patients with visceral neuralgia. For these patients, we placed the catheter in T10 due to the fact that spinal neuralgia was involved in more patients with lower limb pain, and sympathetic nerves and splanchnic autonomic nerves were less likely to be involved, which needs to be addressed by future studies.

In addition to the dose, we noticed that another critical factor for the treatment of MEBTP was the time of onset. Patients involved in this study were patients with lower limb tumors, most of whom had poor healing or infection of incision as they mostly underwent surgery, radiation, and chemotherapy, and targeted therapy. Meanwhile, most of the primary tumors or operative incisions were located in the lumbosacral portion or lower extremities. It was very important for these patients to regularly change position to reduce the incision site pressure, pressure sores, etc. However, the most contradictory thing was the fear of patients due to the active MEBTP, and such patients were unwilling to simply move and change the position, which eventually led to the occurrence of serious complications, such as incision rupture and necrosis, pressure sores, lung infection, etc., and eventually aggravated the development of the disease.

In their randomized controlled study, Brogan et al (16) evaluated an IT drug delivery system vs comprehensive medical management in the treatment of advanced cancer pain and compared it with conventional BTP analgesics, revealing PCIA to be associated with a 3-fold faster onset of action, improved efficacy, and high patient satisfaction. We support their findings. In our study, we found that the onset time of PCIA-controlled MEBTP was significantly shorter (from about 38 minutes to about 8 minutes; $P < 0.05$) (Table 1). ITAPP

dosages were subsequently adjusted according to clinical response, but were not prospectively registered. In our daily clinical procedure, patients were instructed to use the bolus function for predictable MEBTP, and the MEBTP could be well controlled. After doing that, we encouraged patients to take the initiative to change their position, thus further reducing the incidence of pressure sores and other complications. Our study revealed encouraging results, considering the active position change was significantly more frequent than in the past. In addition, the use of non-IT opioids significantly decreased, and the IT use of opioids significantly increased over time. These conclusions were consistent with those of previous studies.

Several studies (27,28) have shown that IT morphine infusion therapy reduces the incidence of the adverse advents caused by systemic opioids due to high morphine concentrations at the site of action. Several operative and drug-related complications may arise after implantation (27,28). Nausea and vomiting, constipation, and respiratory depression were the most frequently reported side effects of opioid administration (28) (Table 5). In our study, there were no significant changes in these effects compared to the preoperative state. As most patients received systemic opioids in this study, some patients suffered from these side effects of opioids, and the fact that we did not observe the relief of these effects after ITAPP may be due to the shorter observation time. Adverse effects of IT morphine therapy are common during the initiation phase of the treatment; however, these effects generally resolve with standard medical management during the first 3 months. On the other hand, we could see that ITAPP did not increase the occurrence of these side effects compared with the traditional treatment. The incidence of drug-related side effects with long-term IT morphine therapy decreases with medical management and dose reduction as therapy continues. Urinary retention following IT morphine administration has an estimated incidence between 42% and 80%. Yet, the incidence of urinary retention with long-term IT morphine therapy has been reported to be 3% (18). In this study, 2 more patients had urinary retention compared to preoperative conditions and were managed by temporary urinary catheterization, which was in accordance with the studies above. Two patients experienced a headache from a cerebrospinal fluid leak after a postarachnoid puncture, which was relieved by conservative treatments. These 2 patients were unable to remain in the supine position, but in the semidecubitus position even after the operation, which may be the important cause of postoperative headache. These symptoms quickly disappeared with fluid rehydration (29).

Limitations

Inevitably, there are still some limitations in our study. First, only 12 patients were retrospectively evaluated. An effective analysis of IT opioid efficacy was not possible because the power of such a small sample size was low. Second, it is a retrospective study without long-term follow-ups, which makes it difficult to assess the long-term complications of ITAPP. Therefore, it was not clear whether opioid-induced side effects were reduced following ITT. Third, we only could use the NRS-11 scoring system to assess pain without including a scale questionnaire and satisfaction survey according to the medical records in a retrospective study, which prevented us from fully evaluating the comprehensive situation of pain improvement. Therefore, we are currently collecting data in a prospective manner, including various quality of life metrics and BTP measurements to further investigate whether ITAPP with PCIA is superior for the management of refractory cancer pain and MEBTP.

Conclusions

The higher PCIA doses and more frequent numbers and predictive administration might lead to overall better results, even for MEBTP in patients with refractory lower extremity cancer pain. ITAPP does not increase the incidence of some adverse advents caused by systemic opioids; however, several operative and drug-related complications may arise in the short term after implantation. A prospective study is urgently needed for a more accurate assessment of the efficacy of ITAPP with PCIA against MEBTP.

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