Intrathecal Analgesia Via a Percutaneous Port For the Management of Movement-Evoked Breakthrough Cancer Pain of Refractory Lower Extremity Cancer Pain: A Retrospective Review and Commentary

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Research Article

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Abstract

Background and Objectives: Intrathecal analgesia (ITA) is a trusty treatment option for refractory and intractable cancer pain. However, there is still no general consensus on the analgesic effect of movement-evoked breakthrough pain (MEBTP) in the ITA setting. This study examined the effect of patient-controlled intrathecal analgesia (PCIA) on analgesic efficacy, emphasizing movement evoked breakthrough pain (MEBTP) in patients with refractory lower extremity cancer pain.

Methods: A retrospective chart review included all patients with refractory lower extremity cancer pain who received Intrathecal morphine infusion therapy via percutaneous port (IMITPP) at our hospital between January 2017 and December 2020. Data on the numerical pain rating scales (NRS) scores, opioid doses, and complications were collected from medical records prior to IMITPP and at a one-month postimplant visit.

Results: A total of 16 patients were included in the study group. Mean SRPI (spontaneous resting pain intensity) decreased from 8.75 pre- IMITPP to 3.75 post- IMITPP, ($P < 0.001$); mean MEPI (movement-evoked breakthrough pain intensity) fell from 8.83 pre- IMITPP to 4.25 post- IMITPP ($P < 0.001$); mean daily morphine equivalent dosing decreased from 360 mg/d to 48mg/d ($P< 0.001$); mean daily morphine equivalent dosing for MEBTP decreased from 87 mg/d to 6 mg/d ($P< 0.001$). Both total and breakthrough dosing of conventional opioid medications significantly decreased following the initiation of ITT with PCIA. The mean perceived time to onset with conventional movement evoked breakthrough medications was 38 minutes, and the mean perceived time to onset with PCIA was 8 minutes ($P < 0.001$).

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

Introduction

Cancer-associated pain continues to present a significant problem, with a prevalence of up to 67% [1]. With the popularization and application of World Health Organization (WHO) “ladder” of pain management, the treatment of cancer pain has made great progress [2, 3]. However, about 20% of patients are still not satisfied with their pain control, even when treatment is standardized according to WHO analgesic ladder [4]. In a prospective study that included 2118 patients with cancer-related pain managed by the WHO analgesic ladder, 3% required intrathecal or epidural analgesia [5]. It is generally accepted that IT therapy provides a safe and efficacious treatment for cancer pain and 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 movement evoked breakthrough pain (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 non-healing, 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 movement evoked BTP on lower limb has been poorly investigated in the ITA setting [15-17].

Due to its relatively lower cost, Intrathecal morphine infusion therapy via percutaneous port (IMITPP) may be a better option for cancer patients with a shorter predicted survival than via an implantable morphine pump [18, 19]. IMITPP is a percutaneous port attached to an external drug infusion pump that allows for continuous intrathecal analgesia for the management of spontaneous resting pain (SRP), patient-controlled intrathecal analgesia (PCIA) for the management of movement evoked breakthrough pain (MEBTP) and/or self-titrate to analgesic effect [16, 20]. In this study, we analyzed the medical records of patients with lower limb cancer pain recently admitted to our hospital, all of whom used IMITPP. We hypothesized that 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. In our study, we performed a retrospective review of patients who received IMITPP to refractory lower extremity cancer pain in China to verify our hypothesis and provide a useful reference for diagnosis and treatment of refractory lower extremity pain caused by a malignant bone tumor.

Materials And Methods

Patient Population

Between January 2017 and December 2020, IMIPTT was performed for 70 patients with advanced cancer pain, 16 of whom were refractory lower extremity cancer pain patients implanted with an intrathecal catheter connected to a percutaneous port (Beijing Yuetong medical apparatus and instruments, Inc, Beijing, China) for IMITPP. Four patients were excluded from the study for the following reasons: 2 patients died within 1 month of catheter implantation; 1 patient who suffered from mania could not use PCIA and follow the requirements; 1 patient underwent notch split because of targeted therapy. Finally, 12 patients were included in the analyses. All procedures were performed by the same physician at the Shougang hospital, Peking University, and under strict sterile operating room conditions with the patient under local anesthesia.

Lumbar subarachnoid puncture and catheterization were performed under X-ray guidance. The soft catheter with metal guide wire was implanted into the subarachnoid space, and the tip of the catheter was placed at T12(The 12th thoracic vertebra) 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 2**). Then, the subcutaneous port was usually placed on the costal margin of the midline of the clavicle on one side, and the catheter was connected to a subcutaneous port via the subcutaneous tunnel. Morphine and bupivacaine diluted with 0.9% sodium chloride solution to 250 mL

(Qinghai Pharmaceuticals, Xining, China) were infused into intrathecal space through the subcutaneous port by an external drug infusion pump (ACEMEDICAL Co., Inc., Gyeoggi-Do, Korea)[21, 22]. The dosing of intrathecal morphine was based on guidelines and clinical experience. Opioids given by traditional routes were then gradually reduced or quickly weaned off before the patients were discharged from the hospital.

Data Collection

All data of this retrospective review were obtained from electronic medical records including patients' demographic data, types of cancer, technical data (such as insertion interspace, catheter tip location), and complications related to IMITPP. Numerical pain rating scales (NRS) scores and doses of opioids before and after IMITPP were also determined. 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 obtained from follow-up appointments. A follow-up visit at 4 weeks after port implantation was selected as the best appropriate time for postimplant data collection. This time period was selected to ensure that postoperative incisional pain did not impact pain assessment and that adequate dose titration of the intrathecal medications was obtained. Medication data before and after port implantation were recorded in medical files of our institution such as the initial evaluation documentation and pharmacy drug reconciliation data for all patients. Following port implantation, the pump was interrogated at each follow-up, and all pump data were recorded in the patient chart.

Statistical Methods

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

Results

Study Population

The final study population included 12 patients who received placement of an intrathecal catheter for cancer pain. All patients could control breakthrough pain 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 1**. Osteosarcoma and fibrosarcoma were the most common types of cancer. Unsatisfied pain control was the most common reason for ITT. Other indications included intolerance of oral or transdermal opioids due to nausea, sedation, or refractory constipation.

All patients were using opioids for control of MEBTP. Mean NRS pain 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 intrathecal regimen at follow-up, are summarized and shown in **Table 1.**

Patient-Reported Pain Scores and perceived time to onset

Between T0 and T1m, the distributions of the worst pain and the perceived time of onset are shown in Figure 1 and Figure 2. Mean SRPI decreased from 8.75 to 3.75; mean MEPI dropped from 8.83 to 4.25; the observed difference was statistically significant ($P < 0.001$). 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 ($P < 0.001$). Further details are shown in **Table 2**.

Nonintrathecal Opioid Medication Use

All except 1 patient who could not tolerate any oral pain medications were on three- step opioid therapy before ITT performance. Before ITT, patients were taking a mean oral morphine equivalent to 360mg/day (range: 90–800 mg/day). Following the catheter placement, the dose was lowered to 48mg/ day (range: 0–120 mg/day; $P< 0.001$). Before ITT, the patients were taking an average of 87mg/day (range: 20–200 mg/day) of oral morphine equivalent short-acting (parenteral, immediate oral release, or oral transmucosal) MEBTP medications for (MEBTP) movement-evoked breakthrough pain (including oxycodone, hydrocodone, morphine, fentanyl, hydromorphone). The dose for MBTP medication decreased to an average of 6mg/day (range: 0–20 mg) following the use of ITT ($P< 0.001$). After the initiation of ITT with PCIA, both total and breakthrough dose for conventional opioid medications significantly decreased. The specific data are summarized in **Table 3**.

Intrathecal Pump Medications

All 12 patients included in our study got a mixture of morphine and local anesthetic (bupivacaine) as an effective part of their intrathecal regimen. Intrathecal drug regimens are summarized in **Table 4**. All patients had the option of using PCIA to treat their breakthrough pain. Patients had a significant increase in intrathecal medication, including morphine and bupivacaine, on postoperative 30 days compared to baseline. The patients were taking an average of Intrathecal opioids from 1.85mg to 27.87mg, including PCIA morphine from 0.65mg to 12.73mg. The patients were taking an average of intrathecal bupivacaine

ranging from 0.94mg to 14.54mg, including PCIA bupivacaine from 0.33mg to 6.48mg. 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 0.99ml/hour. 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 intrathecal 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 post-arachnoid puncture, which was successfully relieved in both patients after conservative treatments. No other complications of intrathecal drug delivery, including catheter kinking, catheter fracture/leakage, catheter migration, 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]. Intrathecal drug infusion therapy is an effective treatment selection for refractory cancer pain; however, the general consensus on its effectiveness for movement evoked BTP has not yet been reached [16, 25]. The purpose of this study was to investigate the efficacy of ITA with PCIA in the treatment of MEBTP of lower extremity tumors.

High cost limited the use of the implanted intrathecal morphine pump despite it is more suitable for long-term use. Recently, intrathecal morphine infusion therapy via a percutaneous port (IMITPP) has become a popular option for refractory cancer pain in some countries for its relatively lower cost [19]. In the present study, we assessed the efficacy and safety of IMITPP.

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 intrathecal drug delivery system versus comprehensive medical management to treat advanced cancer pain, reporting significant improvement in spontaneous resting pain intensity (SRPI). Nonetheless, MEBTP was not adequately controlled despite ITA. However, besides providing support that ITA is a valuable analgesic technique in spontaneous resting pain intensity (SRPI), our results also revealed that movement-evoked BTP could be adequately controlled in patients with lower extremity osteosarcoma and bone metastases. Since the main purpose of this study was to explore movement-evoked BTP, we chose the lower extremity pain with

the greatest impact of movement-evoked BTP. Our results revealed that movement-evoked pain intensity significantly decreased after 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 two studies. In the Bäckryd study [25], their initial dose of intrathecal morphine was adjusted according to pre-ITA doses using an oral-to-intrathecal ratio of 200:1. In the present study, we used the 300:1 ratio, which is in line with the PACC clinical recommendation [26]. Our intrathecal 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 250ml, 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 infused intrathecally. 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 (0.1-0.8mg/ 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 2ml/h, which means that the maximum single bolus dose was 2ml. The lockout period was 10-15 minutes, so our single dose of bolus and the number 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. Patient-controlled intrathecal analgesia 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 otherwise successful ITA.

All patients enrolled in our study were patients with lower limb tumors. More interestingly, in all the cancer pain patients we treated with intrathecal analgesia, lower extremity pain was more significantly relieved compared to patients with visceral neuralgia. For these patients, we placed the catheter in T12 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, and so on. 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 and so on, and eventually aggravated the development of the disease.

In their randomized controlled study, Brogan *et al* evaluated an intrathecal drug delivery system versus 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 [16]. We support their findings. In our study, we found that the onset time of ITA-controlled MEBTP was significantly shorter (from 38min to about 8min; $p<0.05$). ITA 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 movement-evoked pain, 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-ITA opioids significantly decreased, and the intrathecal use of opioids significantly increased over time. These conclusions were consistent with those of previous studies.

Several studies have shown that intrathecal 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]. 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 IMIPTT may be due to the shorter observation time. Adverse effects of intrathecal morphine therapy are common during the initial stage of the treatment; however, these effects usually disappear with standard medical management during the first three months. On the other hand, we could see that IMIPTT did not increase the occurrence of these side effects compared with the traditional treatment. The incidence of drug-related side effects with long-term intrathecal morphine therapy decreases with medical management and dose reduction as therapy continues. Urinary retention following intrathecal morphine administration has an estimated incidence between 42% and 80%. Yet, the incidence of urinary retention with long-term intrathecal morphine therapy has been reported to be 3% [18]. In this study, two 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 post-arachnoid puncture, which was relieved by conservative treatments. These two patients were unable to remain in the supine position but in the semi-decubitus position even after the operation, which may be the important cause of postoperative headache. These symptoms quickly disappeared with fluid rehydration [29].

Inevitably, there are still some limitations in our study. First, only 12 patients were retrospectively evaluated. An effective analysis of intrathecal 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 IMITPP. Therefore, it was not clear whether opioid-induced side effects were reduced following intrathecal therapy. Third, we only could use the NRS 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 breakthrough pain measurements to further investigate whether IMITPP with PCIA is superior for the management of refractory cancer pain and MEBTP.

Conclusion

The higher PCIA doses and numbers and predictive administration might lead to overall better results, even for MEBTP in patients with refractory lower extremity cancer pain. IMITPP 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 IMITPP with PCIA against MEBTP.

Abbreviations

Intrathecal analgesia (ITA) Movement-evoked breakthrough pain (MEBTP) patient-controlled intrathecal analgesia (PCIA) Intrathecal morphine infusion therapy via percutaneous port (IMITPP) Numerical pain rating scales (NRS) Spontaneous resting pain intensity) (SRPI) Movement-evoked breakthrough pain intensity(MEPI)

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Peking university shougang hospital with approval number [IRBW-2021-011-01]. The patient provided written consent. All methods were carried out in accordance with Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and material

All data generated or analysed during this study are included in this published article and its supplementary information files

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Liang Zhou edited the manuscript to its present state and formulated the initial draft of the article. Zhenggang Guo contributed toward conception and provided critical revision of the manuscript.

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Tables

Table1. Baseline patient characteristics

Age, years (mean, standard deviation)	48±8	
Male sex	7/12	
Type of cancer	Osteosarcoma/ fibrosarcoma	bone metastatic tumor
Months since diagnosis (mean)	18(month)	
Reason for IT therapy	poorly controlled pain	intolerance
Pain site	Leg	
Cather tip location	T12	
Morphine nonintrathecal equivalent dose, (mg/day)	360±71mg	
Patients using MEBTP opioids (mg/day)	87±18mg	
Baseline NRS pain score	8±0.3	
Mean duration of intrathecal therapy/months	4±0.8	

IT = intrathecal; NRS = numerical rating scale

Table2. NRS pre- and post-ITT, Onset time for MEBTP

	Pre-implant Mean	Pre-implant Standard deviation	Post-implant Mean	Post-implant Standard deviation	P
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

Table3. Non intrathecal Opioid Medication Use

	N	Pre-implant Mean	Pre-implant Median	Post-implant Mean	Post-implant Median	P
Morphine oral equivalent dose (mg/day)	12	360	322.5	48	40	P<0.05
Breakthrough morphine oral equivalent dose (mg/day)	12	87	80	6	0	P<0.05

Table4. Intrathecal Pump Medications

		baseline dose		Follow up		
		Mean	SE	Mean	SE	
Intrathecal opioid in morphine equivalent dose (mg/day)	12	1.85	0.36	27.87	4.24	P<0.05
Intrathecal l bupivacaine (mg/day)	12	0.94	0.17	14.54	1.55	P<0.05
PCIA opioid in morphine equivalent dose (mg/day)	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/day)	12	13.08	0.41	20.25	0.61	P<0.05

Table5. Opioid-related Side Effects and Technical Complications

Pharmacological side effects	Pre-implant	Post-implant
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

Figures

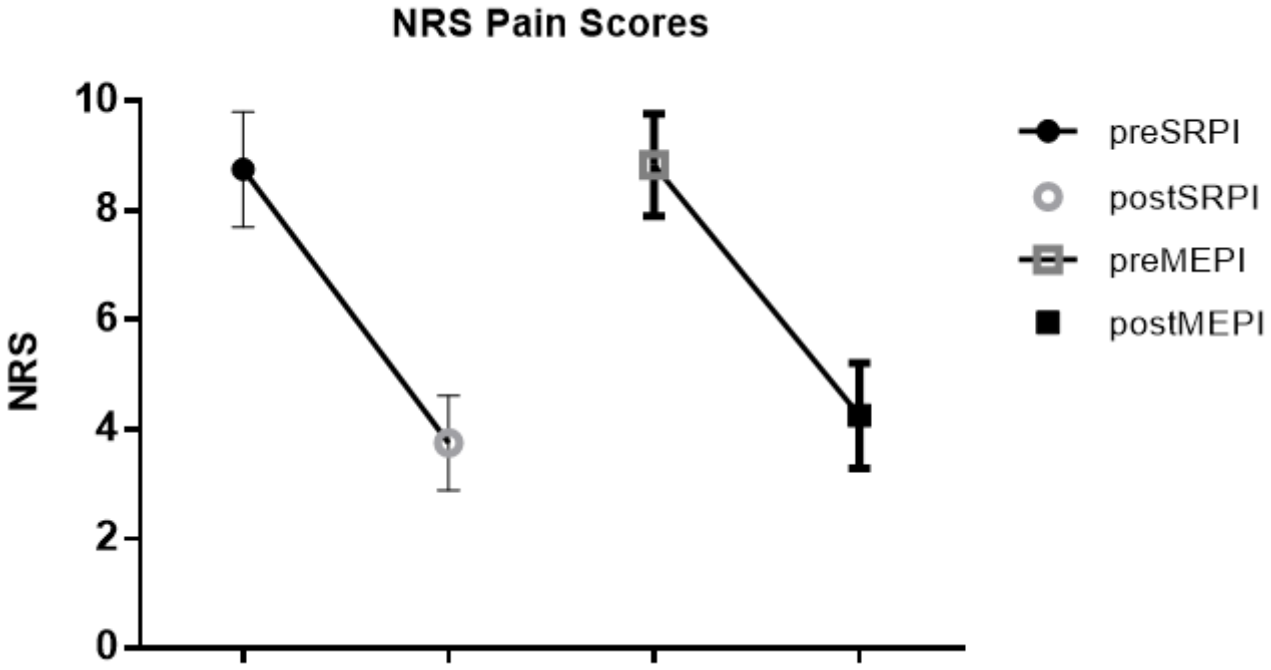

Figure 1

Legend not included with this version

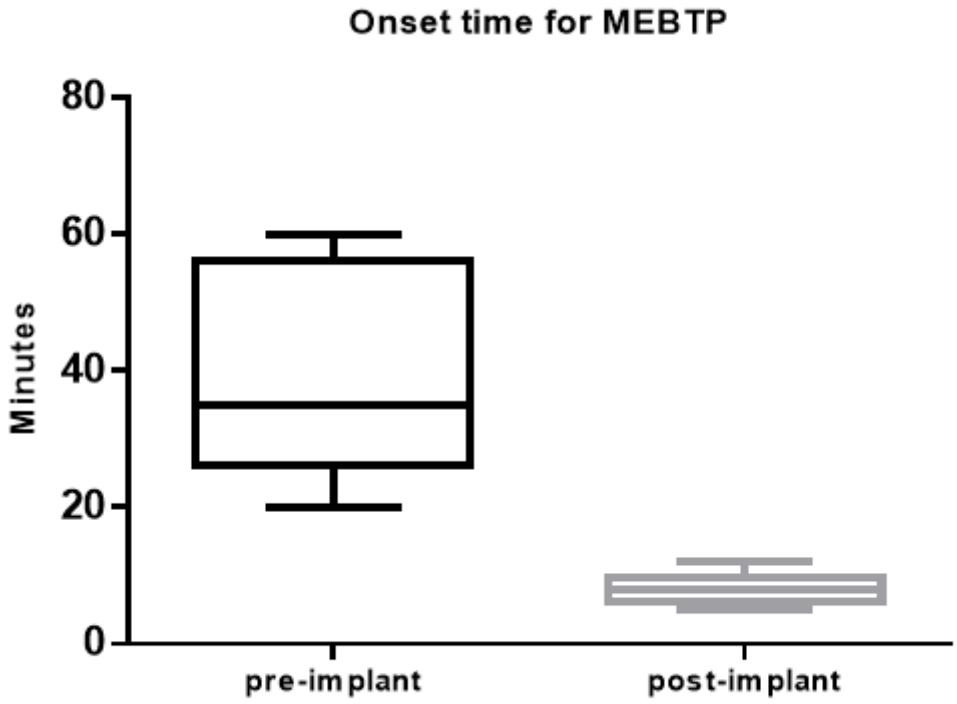

Figure 2

Legend not included with this version