

# Intrathecal morphine combined with ropivacaine induces spinal myoclonus in cancer patients with an implanted intrathecal drug delivery system

## Three case reports

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### Abstract

**Rationale:** Although intrathecal opioid infusion has been used for decades for the treatment of severe pain, myoclonus as one of the complications of this therapeutic modality is now beginning to be recognized more.

**Patients concerns:** Here, we report three patients who developed myoclonus after dose adjustment in intrathecal drug delivery system for the treatment of refractory cancer pain.

**Diagnosis:** Spinal myoclonus is a sudden, brief, shock-like muscle contractions originating from the central nervous system.<sup>[1]</sup> In our cases, it occurred after opioid administration via intrathecal delivery system with no abnormality found in laboratory or imaging examinations.

**Interventions:** Spinal myoclonus can be treated effectively by reducing the dose or infusion rate as described in case 1, or changing from an intrathecal to systemic administration in case 2, or correcting infusion and bolus parameters mistakes in case 3.

**Outcomes:** All patients recovered quickly after stopping or decreasing the intrathecal drug infusion.

**Lessons:** Prevention is more important than treatment as for spinal myoclonus. Pain management teams should be aware of this distressing complication. Dose of intrathecal drugs should not exceed the recommended maximal daily doses by guidelines and patient education is important for successful intrathecal analgesic therapy.

**Abbreviations:** NRS = numerical rating scale, PCA = patient-controlled analgesia.

**Keywords:** intrathecal, morphine, myoclonus

## 1. Introduction

Pain is a common feature of advanced malignancy. However, 10% to 30% of cancer patients with limited life expectancy either cannot obtain adequate pain relief through conservative routes of

analgesic administration or would experience serious side effects related to opioids use under the 3-step approach espoused by the guidelines established by the World Health Organization.<sup>[2]</sup> For those patients, intrathecal drug delivery is an alternative intervention for more effective pain management, less side effects,<sup>[3]</sup> and improved quality of life.<sup>[4]</sup>

Although intrathecal opioid infusion has been used for decades for treating severe pain, the complications of this therapeutic modality are now beginning to be recognized more thoroughly, especially pharmacologic reactions. Opioid-related myoclonus, as one of the opioid-related neuromuscular symptoms, has been reported in patients receiving systemic or local administration of opioids.<sup>[5,6]</sup> Morphine has been considered as the gold standard for intrathecal drug delivery because of its stability, strong receptor affinity, and extensive user experience of the drug. However, there have been several reports documenting development of spinal myoclonus following intrathecal administration morphine alone.<sup>[7,8]</sup> Glavina and Robertshaw<sup>[8]</sup> reported myoclonic spasms induced by intrathecal morphine and subsequent treatment with 3 ml of plain 0.5% bupivacaine injected intrathecally.

Here, we report 3 patients who developed spinal myoclonus after intrathecal delivery of morphine combined with ropivacaine for refractory cancer pain. This case series was approved by the ethics committee of the First Affiliated Hospital, Zhejiang University School of Medicine and the First People's Hospital

Editor: N/A.

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

This research was supported by the National Natural Science Foundation, Beijing, China (Grant no. 81603198) to Dr Zhiyou Peng.

The authors declare that they have no conflicts of interest.

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Medicine (2019) 98:18(e15330)

Received: 17 October 2018 / Received in final form: 19 March 2019 / Accepted: 25 March 2019

<http://dx.doi.org/10.1097/MD.00000000000015330>

of Yuhang District, Hangzhou. Informed written consent was obtained from the patients or their family for publication of this article.

## 2. Case presentation

### 2.1. Case 1

A 48-year-old female lung cancer patient with metastasis to the thoracic vertebral body, pleura, and rib, presented with worsening back and left chest wall pain, refractory to conventional medical management, including a fentanyl transdermal patch 16.8mcg q72 hours, gabapentin 600mg tid and celecoxib 200mg bid. The patient experienced severe vomiting due to the side effects of opioid medication. An intrathecal delivery drug system was then implanted, with no complications, on March 24, 2015, with the tip of the intrathecal catheter placed at the T6 level. The tunneled catheter was subsequently connected to an external patient-controlled analgesia (PCA) device. With reference to the Polyanalgesia Consensus Conference 2012<sup>[9]</sup> publication, a combination of local anesthetics and morphine was used to treat her cancer pain syndrome. Based on her previous opioid dosage, the patient was started with a mixture of 1 mg/ml morphine and 1.25 mg/ml ropivacaine in normal saline as a 0.5-ml bolus injection with a 2 hours lockout interval. After achieving sufficient pain relief (numerical rating scale [NRS]  $\leq 3/10$  and breakthrough pain  $\leq 3$  times a day) and improvement in side effects ( $\geq 50\%$  reduction), she was discharged and referred to outpatient follow-up and further management. The total intrathecal dose of morphine was 1.5 mg per day at first and the dosage was gradually increased, titrated to her pain intensity.

Three months after the implantation surgery, the patient was readmitted due to progression of the disease, with unbearable breakthrough pain in the original location, 7/10 on the NRS, despite an intrathecal infusion at a rate of 0.2 ml/h continuously, along with a 1 ml bolus injection with a 1-hour lockout interval through the external PCA (1.5 mg/ml morphine and 1.25 mg/ml ropivacaine in normal saline). The total intrathecal dose of morphine was approximately 16.2 mg per day. After admission, we increased the morphine concentration to 3 mg/ml without a change in the ropivacaine concentration (0.125%), which alleviated her increased pain. Unfortunately, 12 hours after this adjustment, the patient developed sudden episodic myoclonus of the lower limbs, without loss of consciousness or changes of muscle strength. Each spasm lasted 5 to 10 seconds and occurred at 10 to 30 seconds intervals. All muscle groups in the lower legs and perineum were affected. These spasms caused the patient distress and discomfort in the lower limbs and perineum area. Laboratory tests, including a metabolic panel, hepatic and renal function tests, and continuous electrocardiogram were recorded and returned to normal. There was no sign of cerebral epileptic activity or respiratory depression. Two doses of intravenous diazepam 10 mg failed to stop the spasm. Eventually, the intrathecal infusion rate was reduced to preadmission levels, and the spasms lasted for an additional 5 hours, after which it gradually subsided. A lumbar spine magnetic resonance imaging was ordered 1 day later, which showed no sign of interval changes or metastatic compression to the spinal cord. An additional fentanyl patch was added to the treatment regimen to help control pain with intrathecal morphine no more than 15 mg. No additional myoclonus spasm was observed in subsequent follow-up until the patient eventually passed away after multiple organ failure 3 months later.

### 2.2. Case 2

A 62-year-old female patient with a medical history of endometrial adenocarcinoma, whose primary tumor resection 5 years earlier, experienced tumor recurrence with an abdominal mass measuring  $12 \times 15 \times 10$  cm, along with metastatic lesions to the vertebral body, complicated by multiple segmental compression fracture. She presented to us with severe pain, refractory to conventional oral medical pain management, including oxycodone 120 mg q12 hours, gabapentin 900 mg tid and flurbiprofen axetil 50 mg bid. There was no prior history of epilepsy or other neurological diseases. Subsequently, intrathecal drug delivery system was implanted with the tip of the intrathecal catheter placed at the T7 level at 1 hospital in Zhejiang Province. The patient was given an external PCA pump contained 1 mg/ml morphine in normal saline, with the infusion rate set at 1 ml bolus injection each time, with a 2 hours lockout interval. The total intrathecal dose of morphine was about 3 mg per day at first, and then gradually increased with titration to pain control. Unfortunately, her pain persisted even when the morphine dosage was increased to 12 mg/d by 1 month later. She was then offered adjustment by adding ropivacaine 1.25 mg/ml to the 1 mg/ml morphine solution, as well as adding continuous infusion at 0.2 mg/h in addition to the bolus injection at 1 ml each time, with a 1-hour lockout interval. Her severe pain persisted even at a continuous infusion rate increased up to 1.0 ml/h, along with a 1.5 ml bolus injection with a 1-hour lockout interval over the next 2 weeks. Spinal myoclonus occurred at the time the total dose of morphine reached 45 mg and ropivacaine reached 22.5 mg per day. Frequent symmetric spastic contractions in the lower limb muscles began. The duration of spasms was 6 to 8 seconds on average and occurred at about every 30 seconds. Uncontrollable twitching and jerking of the muscles exacerbated her pain and caused further distress. The patient's heart rate, respiration rate, oxygen saturation, and muscle strength remained stable. Laboratory findings included a complete blood count, metabolic panel, hepatic and renal function, and electrocardiogram were recorded and showed normal findings. Midazolam 10 mg total and sodium valproate 0.4 mg/40 ml was given immediately through slow intravenous injection without improvement. Subsequently, her intrathecal infusion dosage was reduced to half and her spasm subsequently resolved. Additional intravenous medication through a morphine PCA was then added to assist in control of her pain, along with her intrathecal morphine infusion set to below 30 mg per day and ropivacaine to  $\leq 15$  mg per day, until the patient died from multiple organ failure 3 weeks later.

### 2.3. Case 3

A 53-year-old female patient with metastatic left breast cancer with lesions to the liver, iliac vessels, right lung, right ilium, and S1 to S3 vertebral body, presented with worsening right hip, back, and left chest wall pain, which was refractory to an oral pain medication regimen, including oxycodone 280 mg q12 hours and gabapentin 900 mg tid. The patient underwent intrathecal drug delivery system implantation with an external electronic pump without complications, on May 20, 2016, at Yuhang No. 1 Hospital, Zhejiang Province. Considering her severe cancer pain presentation and her high opiate use, she was tried with continuous infusion at 0.2 ml/h of a mixture of morphine 1 mg/ml and ropivacaine 1 mg/ml in normal saline, with a 0.2 ml

bolus injection with a 2-hours lockout interval. The pain was alleviated significantly, and the benefit sustained with an average NRS of 3/10 and breakthrough pain 3 times a day. One month later, when she presented for refill, the infusion and bolus parameters were mistakenly set to 2 ml for both bolus rate and continuous infusion rate by 1 registered nurse. Six hours after the refill, during which 12 mg morphine and 6 mg ropivacaine were delivered intrathecally, the patient developed numbness and muscle weakness; her muscle strength decreased from 5/5 to 3/5, and she had more pain, as well as convulsions in her lower extremities. The spinal myoclonus initially occurred every 40 to 60 seconds, but gradually increased in frequency and intensity. The patient was sent to the hospital by her family. The pump was subsequently stopped as soon as the mistake was found. Two hours later, the convulsions resolved. However, muscle strength of the lower extremities did not recover until 12 hours later. The patient passed away 1 month later respiratory failure with no further similar episode.

### 3. Discussion

Although mostly occurring at higher doses or concentrations,<sup>[5]</sup> opioid-related myoclonus has been reported after administration of a variety of doses, various durations of treatment, and routes of administration of different opioids.<sup>[10,11]</sup> Intrathecal drug delivery system is currently commonly recommended for chronic refractory pain, especially for cancer pain. The prescription of morphine for intrathecal drug delivery system has increased significantly, so has the incidence of neuromuscular side effects (myoclonus, allodynia, seizures).<sup>[12]</sup> Compared to systemic administration, spinal myoclonus following intrathecal morphine is rare, and there have been only a few reports.<sup>[8,13–15]</sup> These cases series spanned three different hospitals over a 3-year period. To our knowledge, the development of spinal myoclonus after administration of a large dose of morphine combined with ropivacaine by intrathecal infusion therapy has not been reported to date.

Spinal myoclonus is a nongeneralized neuromuscular dysfunction that may be focal or segmental, affecting single muscles or muscle groups. The suggested pathophysiology of spinal myoclonus includes abnormal hyperactivity of local anterior horn neurons, aberrant local axon re-excitation, loss of inhibitory function of local dorsal horn interneurons, and loss of inhibition from suprasegmental descending pathways.<sup>[16–18]</sup> Spinal myoclonus usually results from spinal cord pathology, such as compression, sepsis, degeneration, vasculopathy, or neoplasm, and so on.<sup>[16]</sup> It may also be associated with epilepsy, toxicity, drug reactions, intrathecal analgesics/anesthetics, or intrathecal contrast material.<sup>[16,18]</sup>

For our patients, tumor compression, sepsis, and trauma could be excluded, because they recovered quickly after stopping or reducing the intrathecal dose. In addition, indwelling spinal or epidural catheters may cause myoclonus by irritating the spinal cord or nerve roots.<sup>[19]</sup> This reason could also be excluded by the rapid improvement of their condition without removal of the catheters. The patients did not have any electrolyte disorder or renal dysfunction, which may have predisposed them to neurological dysfunction.

The mechanisms of spinal myoclonus remain to be determined. It is reported that myoclonus is always associated with extremely chronic and high concentrations of plasma morphine and metabolites.<sup>[20]</sup> A high dose of intrathecal morphine, exceeding the recommended maximum dose per day, was thought to be a

major factor in the development of spinal myoclonus in our 3 cases. Local anesthetics block nerve impulses and provide a degree of nociceptive, sensory, and motor nerve block. Patients in this case series experienced severe neuropathic or mixed neuropathic–nociceptive cancer pain, therefore a combination of morphine with ropivacaine may be better than morphine alone. Glavina and Robertshaw<sup>[8]</sup> have reported that 3 ml of plain 0.5% bupivacaine for intrathecal injection completely abolished the spasms induced by intrathecal morphine. However, some researchers suggested that local anesthetic neurotoxicity may also cause spinal myoclonus.<sup>[21]</sup> The inhibitory effects of a local anesthetic may cause increased irritability of  $\alpha$ -motor neurons, leading to the development of myoclonus.<sup>[22,23]</sup> Moreover, spinal injection with ropivacaine has been shown to decrease local spinal cord blood flow.<sup>[24]</sup> Alfa et al<sup>[25]</sup> reported that local anesthetic injected via intrathecal routes could also cause spinal myoclonus. Therefore, ropivacaine, which was used in these cases and well-known to be the least neurotoxic of the available local anesthetics,<sup>[26]</sup> could not be ruled out as a cause for the spinal myoclonus. Although difficult to prove, an overdose of morphine combined with ropivacaine intrathecally may have been a major contributory factor to the spinal myoclonus in these cases.

Treatment of spinal myoclonus includes detection of the etiology, abolition, or minimization of this etiology, and symptomatic treatment with benzodiazepines, anticonvulsants, or skeletal muscle relaxants.<sup>[3,27,28]</sup> In our cases, spinal myoclonus was treated successfully by stopping or decreasing the intrathecal drug infusion.

Preventions of myoclonus after implantation of intrathecal drug delivery system are as follows. The intrathecal drug doses should not exceed the maximal daily doses recommended by the 2012 and 2017 Polyanalgesia Consensus (15 mg/d for morphine, 15–20 mg/d for bupivacaine, except for end-of-life care). Once the recommended maximum dosage has been reached, opioids should be rotated or the drugs should be adjusted from first line to a lower level, with adoption of multimodal analgesia. If intractable pain can still not be alleviated by changing opioids or by combining it with local anesthetics, systemic administration (oral, intravenous, or transdermal drug delivery) is recommended. Medication errors should be avoided. The external pump should be locked and should not be titrated easily by patients or their family members. Drug refill programming must be done by trained personnel and rechecked by another doctor or nurse, who can actually assess pain and subtle changes in the patients' condition. Moreover, factors possibly contributing to the myoclonus should also be assessed carefully when considering patients for intrathecal drug delivery system. These include renal dysfunction, antidepressant drug use, and chronic steroid therapy. When starting patient on this treatment, spinal spasms, and other complications could be diminished or eliminated by slow titration of medications. Patient education is key to successful intrathecal analgesic therapy: patients should be constantly reminded of the active role they play in their own therapy, as well as to report to the medical team in case of any change in their medical condition.

### 4. Conclusion

In conclusion, although spinal myoclonus following intrathecal drug delivery system is rare, it can cause physical and psychological distress to patients and the pain management

teams should be aware of it. We suggest that prevention is more important than treatment as for this clinical symptom.

### Author contributions

**Data curation:** Yixin Yang, Yimin Zhao.

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