



Educational case report

Management of patients with pain and severe side effects while on intrathecal morphine therapy: A case study

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HIGHLIGHTS

- Intrathecal morphine therapy is deemed the last resort for chronic pain.
- Two patients experienced severe side effects and lack of optimal pain control.
- Treatment using a multidisciplinary approach and opioid tapering was effective.

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ABSTRACT

Background and aims: The use of intrathecal morphine therapy has been increasing. Intrathecal morphine therapy is deemed the last resort for patients with intractable chronic non-cancer pain (CNCN) who failed other treatments including surgery and pharmaceutical interventions. However, effective treatments for patients with CNCN who “failed” this last resort because of severe side effects and lack of optimal pain control remain unclear.

Methods and results: Here we report two successfully managed patients (Ms. S and Mr. T) who had intractable pain and significant complications years after the start of intrathecal morphine therapy. The two patients had intrathecal morphine pump implantation due to chronic consistent pain and multiple failed surgical operations in the spine. Years after morphine pump implantation, both patients had significant chronic pain and compromised function for activities of daily living. Additionally, Ms. S also had four episodes of small bowel obstruction while Mr. T was diagnosed with end stage severe “dementia”. The successful management of these two patients included the simultaneous multidisciplinary approach for pain management, opioids tapering and discontinuation.

Conclusion: The case study indicates that for patients who fail to respond to intrathecal morphine pump therapy due to side effects and lack of optimal pain control, the simultaneous multidisciplinary pain management approach and opioids tapering seem appropriate.

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1. Introduction

The clinical use of intrathecal morphine was firstly introduced as continuous spinal analgesia for obstetric analgesia in 1979 [1,2]. This was followed by the introduction of programmable intrathecal morphine pump (PIMP) for pain related to malignancies in 1981 [3,4]. The PIMP devices allow for non-invasive dose changes and

refills and can decrease adverse effects of opioids such as sedation and constipation [4]. Since the 1980s, the use of intrathecal morphine therapy has been increasing [5], and has been expanded to the treatment of patients with intractable chronic non-cancer pain (CNCN) who failed other treatments including surgery and pharmaceutical interventions [6]. The increase in intrathecal morphine therapy use is supported by its effectiveness and ease of use, although large randomized control trials are still lacking [5,6].

Intrathecal morphine therapy is deemed the last resort for patients with CNCN. However, years after morphine pump implantation, adverse events of morphine, sometimes including small bowel obstruction and severe sedation, respiratory depression and even death, may become increasingly common [7]. Additionally,

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studies also found that patients with chronic morphine use may present with poor pain control, decreased quality of life, and frequent emergency room visits, all of which are common side effects from chronic morphine use [8,9].

While the emergent management of the patient with pain and severe side effects while on long-term intrathecal morphine therapy focuses on life saving with opioid antagonist for side effects and/or bolus opioid injection for pain, optimal management of these patients may include tapering of intrathecal morphine and the management of CNCP. Methadone taper is the most commonly used method for opioid tapering where patients on long-term opioids are firstly stabilized with a dose of methadone that mitigates withdrawal followed by gradual opioid taper [10]. For CNCP itself, a multidisciplinary approach is usually recommended [12]. Nonetheless, research studies on combining methadone taper with a multidisciplinary pain management approach for patients with pain and severe side effects while on long-term intrathecal morphine therapy are still scarce in the literature, and optimal treatments for these patients remain unclear. Here we report two patients with intractable pain and significant complications while on long-term intrathecal morphine therapy. The two patients were successfully treated with methadone taper in combination with the multidisciplinary pain management.

2. Case presentation

2.1. Case 1

Ms. S was 67 years old when she had the PIMP implantation for her prolonged consistent low back pain in 2004. Prior to that, Ms. S had 4 failed back surgeries and received the implantation of an implantable spinal cord stimulator. After the PIMP implantation, Ms. S was also given oxycodone and hydrocodone for breakthrough pain. With the highest intrathecal morphine dosage of 3.60 mg/day and bolus morphine dosing, the treatment protocol had become unsatisfactory as Ms. S had increased visits at hospital emergency departments for respiratory compromise-induced pneumonia, small bowel obstruction, constipation, on top of intolerable pain aggravation.

By the end of 2009, Ms. S restarted to use fentanyl patch with increasing doses as she believed that morphine no longer worked for her, despite the continuous treatment of intrathecal morphine. From 2009 to 2011, Ms. S received three additional surgeries for her back pain. In October, 2011, Ms. S was admitted to the hospital due to facial numbness, tingling, and sensory changes with anxiety and intractable lower back pain. We saw the patient on October 20th, 2011 for pain management and rehabilitation.

By that moment, Ms. S had been unable to sit or stand and had difficulties in transferring in and out of bed for more than two years. Besides morphine per pump (3.60 mg/day), Ms. S was also receiving fentanyl patch 50 mcg/h for pain control. After relevant examination and lab work, Ms. S was diagnosed with anxiety, trochanteric bursitis as well as lumbosacral radiculopathy and plexopathy. We thus treated the patient with bursa injection and lumbosacral plexus block. We also recommended methadone (2.5 mg, twice a day) for the tapering of both intrathecal morphine and fentanyl. After three days of methadone use, we discontinued fentanyl patch and increased methadone to 5 mg three times daily. We then decreased the dosing of morphine (initially 20% decrease monthly) while slightly modulating the dosing of methadone (5 mg given three to five times a day depending on patient's response).

Meanwhile, we adopted a multidisciplinary approach for pain management which included patient education and counselling, therapeutic exercises, fluoxetine, clonidine, lamotrigine, mirtazepine, and alternative and complementary medicine [heating

and cold pad, acupuncture, and massage when appropriate]. Additionally, short-term meloxicam, naproxen, oxcarbazepine, and pregabalin had also been used separately or in combination during the long treatment course. We completely discontinued Ms. S's morphine per pump and started methadone weaning on June 27th, 2013. We slowly decreased methadone quantity and then frequency. By the time patient took methadone for the last time on July 20th, 2014, Ms. S's pain was well controlled and she was able to stand, sit, walk with rolling walker, and drive for community activities. She underwent another operation to remove her morphine pump in late 2014 after pain was under control with exercise and other non-opioid medications for around five months.

2.2. Case 2

Mr. T was 65 years old in 2004 when he had the PIMP implantation after multiple failed back and cervical surgeries for his work related injuries. Although the morphine pump originally provided some help, his pain over the lumbar and cervical spine increased over time. Since 2006, Mr. T had been receiving intrathecal morphine 3.373 mg/day and bupivacaine 0.8432 mg/day with the use of additional oral hydrocodone, oxycodone and hydromorphone for pain control. Mr. T had gradually lost his ability to stand and walk, and became totally wheelchair bound. Additionally, he also had gradually developed confusion, agitation, delirium, bowel and bladder incontinence, and frequent episodes of hypoxaemia from 2006 to 2011. In early 2011, Mr. T was diagnosed with end stage severe "dementia" and was under hospice care at a nursing home. On March 1st, 2012, Mr. T was brought in our office by her family for a second opinion.

After a close examination and evaluation, we found it was not sufficient to diagnose Mr. T with dementia while he was on large doses of opioids. We recommended weaning down the opioid medications using methadone taper while managing Mr. T's pain with the comprehensive multidisciplinary approach. Similar to the aforementioned case, we decreased the dosing of morphine (initially 20% decrease monthly) while slightly modulating the dosing of methadone (5 mg given three to five times a day depending on patient's response) after initially 2.5 mg twice a day for one week tolerance (allergy) test. Additionally, treatments including family education and counselling, physical therapy, tapering dose of methadone as well as adjuvant medications such as clonidine, lamotrigine, mirtazepine, oxcarbazepine, and citalopram were used.

During the methadone taper process, Mr. T's dementia-like symptoms improved gradually. By the summer of 2012, Mr. T was discharged home from nursing home. With pain well-controlled, on November 29th, 2012, we stopped the use of morphine per pump and started gradual methadone weaning via slowly decreasing methadone quantity and then frequency. On April 11th, 2013, his methadone use was completely discontinued when Mr. T had been tolerating well with standing and walking training with therapists, had no pain for most of the time, and was also able to ambulate with rolling walker inside his house with dementia-like symptoms completely resolved. The pump was later removed in early 2014.

3. Discussion

Both patients had unsatisfactory pain control and general weakness after years of opioid use. The suppressed endogenous opioid peptide system may be one of the potential culprits. The human body is constantly secreting endogenous opioid peptides [13]. The endogenous opioids participate in various physiological activities including the secretion of various hormones [13,14]. Van Bockstaele [15] reported decrease in endogenous opioid peptides in the rat medullo-coerulear pathway after chronic morphine treatment.

Additional side effects from intrathecal morphine may include the frequent emergency room visits and hospitalization in Ms. S and the nursing home stay because of severe sedation (“dementia”) in Mr. T.

Unsatisfactory pain control and concerning side effects exceeding benefits are indications for opioid tapering [11]. For the presented two patients, clinicians need to focus their plan of care to the simultaneous pain management with opioid tapering. Chronic pain involves the complex and dynamic interactions among psychological, social, and physiological factors [12]; therefore, management of patients with chronic pain should include a comprehensive multidisciplinary approach to maximize benefits, reduce side effects, and expedite recovery [16]. For successful opioid tapering, important pharmaceutical treatments in these situations including clonidine to decrease withdrawal effects, antidepressants to manage anxiety and depression, lamotrigine for mood stabilization and potential neurogenic pain may be used separately or in combination [17].

Opioid medications are divided into long and short acting opioids depending on their half-lives [18]. Morphine has a half-life of 2–3 h; methadone has a half-life of 24 h [18]. Short-acting opioids may be more likely to cause fluctuations in the functions of the available opioids (endogenous opioid peptides and externally given opioids) in the human body because of their short half-lives and requirement for more frequent dosing [18]. These fluctuations of opioids might be causing alternating pain and happiness in patients [14] and thus anxiety and depression, which in turn aggravate the symptom fluctuations. Because of drug seeking, patients may have increases in opioid dosing quantity and frequency, more so in patients on short-acting opioids [19]. Upon many occasions, clinicians use other short-acting opioid medications (like oxycodone, hydrocodone, hydromorphone, morphine) for breakthrough pain or uncontrolled pain after morphine pump implantation. Peripheral and/or central sensitization (hyperexcitability) have been suggested to be related to the development of breakthrough pain which is defined as transient worsening of pain in patients with an ongoing steady pain [20]. While short-term use of short-acting opioid medications may be necessary, the long-term use of additional opioids in patients with morphine pump implantation should be highly cautious. Chronic short-acting opioid use may create more fluctuations of symptoms in patients [18].

Additionally, the unsatisfactory pain control in intrathecal morphine therapy may be related to the development of opioid dependence and tolerance as functions of the endogenous opioid peptides and/or their receptors may decrease in the human body [15,19]. Worse still, hyperalgesia which is related to decreased balance point (threshold) for pain and increased balance point (threshold) for happiness after long term exogenous opioid use is also common [19]. Because of the fluctuations in symptoms [18], hyperalgesia may be more prominent, if additional long-term short-acting opioids are used on top of intrathecal morphine therapy. After morphine pump implantation, both patients gradually developed significant uncontrolled pain, side effects, and compromised function of activities of daily living while on relatively large dose (3.60 mg/day and 3.373 mg/day) intrathecal morphine therapy with multiple other short-acting opioid medications.

Methadone is the traditional long acting opioid conferring reliable absorption and steady effects over two to three days [18]. Methadone is the traditional medication used in medication assisted treatment for opioid use disorders [18]. With the use of long-acting opioids like methadone, we may minimize the fluctuation of symptoms while conferring more steady levels of opioids inside the human body. Additionally, as a result of the longer half-life of methadone, dependence may take longer to develop and pain and mood are more likely to be kept relatively stable. With better baseline and stable pain control, the transitional use of methadone

in opioid tapering will also decrease the risk of anxiety in patients [19]. Tapering of the transitional methadone and intrathecal morphine requires the continuous application of the multidisciplinary pain managements including adjuvant medications like clonidine, a commonly used medication for withdrawal symptoms. The last 2.5 mg per day of methadone was usually difficult to taper. The tapering of methadone in Ms. S took one year and took longer than four month in Mr. T. Nonetheless, methadone taper for discontinuing intrathecal morphine seems possible.

Admittedly, we should be cautious when using methadone taper with the comprehensive multidisciplinary approach for the management of patients who failed intrathecal morphine pump therapy. First, large variability in methadone half-life (10–60 h) and potential for delayed toxicity have been described for methadone [21]. Second, the combinational use of adjuvant medications raises concerns for polypharmacy which increases the risk of drug interactions and side-effects [22].

4. Conclusion

For patients with intractable chronic pain and significant complications while on long-term intrathecal morphine therapy, the simultaneous multidisciplinary pain management approach and methadone taper seems appropriate for these conditions.

Conflict of interest

No actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

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