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Spinal Opiods

Key Points

- Spinal opioid bioavailability is inversely proportional to drug lipid solubility.
- Sedation and respiratory depression are the most serious adverse effects of opioid-induced analgesia, and are the greatest causes for concern for clinicians. There are no clear correlations between opioid dose and adverse effects in the acute pain setting.
- Despite the widespread use of intrathecal opioids, there is still no clear evidence or consensus among anaesthetists regarding the optimal dose of intrathecal opioids for postoperative pain relief.

MCQ

True or False:

1. Analgesia via neuraxial opioid administration is primarily mediated by binding of pre- and postsynaptic opioid receptors in laminae I and II of the dorsal horn of the spinal cord.
2. Compared to morphine, diamorphine has a slow onset (up to 60 minutes) and a significantly longer duration of action, with a high possibility of delayed respiratory depression.
3. The National Institute for Clinical Excellence (NICE) recommends diamorphine 0.3–0.4 mg for analgesia after elective Caesarean section
4. There is a significant variability in the dose of intrathecal diamorphine used (range: 0.1–2 mg), with < 0.5 mg used for laparoscopic colorectal surgery in the majority of individuals.
5. Concurrent administration of systemic opioids has no effect on the incidence of respiratory depression following intrathecal opioid administration.

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Introduction

Effective multi-modal analgesia enhances patient satisfaction, facilitates early mobilisation and return to function after major surgery, and is an important component of Enhanced Recovery After Surgery (ERAS) programmes. In recent years, there have been numerous major advances in surgical techniques, and there is increasing interest in minimally invasive techniques within the framework of ERAS. There is also a great deal of interest in alternate methods of pain relief, including spinal opioids and local anaesthetic blocks. A previous survey (2014) of ERAS-UK Society members indicated that 59% of institutions preferentially use spinal opiates for laparoscopic procedures. In a survey of 270 anaesthesia departments across United Kingdom, diamorphine was identified as the most commonly used intrathecal opioid, followed by fentanyl [1]. Despite the widespread use of intrathecal opioids, there is still neither clear evidence, nor a consensus among anaesthetists, regarding the optimal dose of intrathecal opioids for postoperative pain relief. This review examines some of the key aspects of the use of intrathecal opioids for acute postoperative analgesia.

History

The use of intrathecal opioids dates back to 1901, when the Romanian surgeon Nicolae Racoviceanu-Pitesti presented his experience of using intrathecal opioids (a mixture of cocaine and morphine) in Paris. Pert and Snyder discovered the opioid receptors in 1973, and opioid receptors were subsequently identified in the dorsal horn of the spinal cord by radioligand techniques in 1977 [2]. In 1979, Wang et al. described the use of intrathecal morphine in eight patients with genitourinary malignancies [3]. Since then, the use of intrathecal opioids has been widely accepted for postoperative analgesia. Morphine was the first opioid approved by the US Food and Drug Administration (FDA) for intrathecal use.

Mechanism of action

Opioids are agonists of opioid receptors, which are widely expressed in the brain and spinal cord. There are four main classes of opioid receptor, i.e. mu, kappa, delta and nociception, all of which are G protein-coupled receptors. Analgesia induced by neuraxial opioid administration is primarily mediated by binding of pre- and postsynaptic opioid receptors in laminae I and II of the dorsal horn of the spinal cord. Receptor activation leads to G protein-mediated potassium channel opening (mu and delta) and calcium channel closure (kappa), with an overall reduction in intracellular calcium. This reduces the release of excitatory transmitters (glutamate and substance P) from presynaptic C fibres, but not fibre terminals, with consequent reduction in nociceptive transmission [2]. Binding of opioids to

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postsynaptic receptor sites in the dorsal horn results in potassium channel opening and indirect activation of descending pathways from the brainstem [2]. The effect of opioids on the dorsal horn, i.e. a specific analgesic action without sensory, motor or autonomic effects, is termed selective spinal analgesia [4].

Other suggested mechanisms of action include adenosine-mediated hyperpolarisation of nerve fibres and reduced release of GABA from the dorsal horn; there are clear structural similarities between lipophilic opioids and local anaesthetic agents.

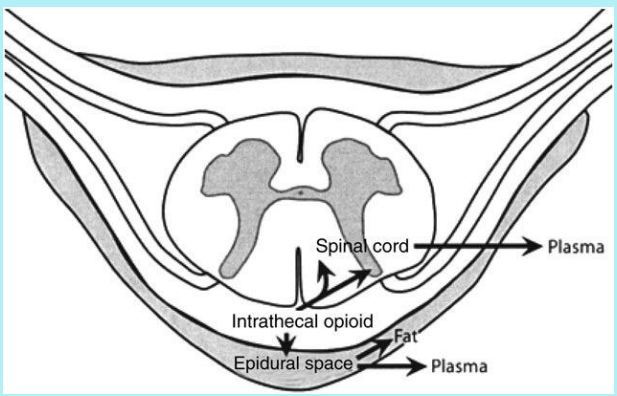
Pharmacodynamics and pharmacokinetics

The pharmacokinetics of intrathecal opioids are complex, and be described by a multi-compartmental model (Fig. 1). They are determined by the physicochemical properties of the opioid used and the cerebrospinal fluid (CSF) dynamics. Once injected intrathecally, opioids can act as ligands on opioid receptors in three different areas to produce analgesia:

1. They have direct access to the dorsal horn of the spinal cord (their main site of action).

2. They are transported supraspinally by bulk CSF flow.

3. Small amounts of opioid diffuse into the epidural space followed by systemic absorption. Intrathecal opioids undergo minimal metabolism within the CSF.



The physicochemical properties of intrathecal opioids determine their onset time, duration of action and potency. High lipid solubility and low p*K*a of an opioid result in high potency and a rapid onset of effect, but with limited duration of action, although decreasing lipophilicity increases the duration of action [2]. Highly lipid-soluble (lipophilic) opioids, such

as fentanyl and sufentanil, diffuse into the spinal cord and rapidly bind to receptors in the dorsal horn. This produces a rapid onset of analgesia with minimal cephalad spread and, subsequently, a low risk of delayed respiratory depression. However, the duration of analgesia is relatively short. Morphine is poorly lipid-soluble (hydrophilic), and binds dorsal horn receptors much more slowly compared to fentanyl, resulting in slower-onset, but more prolonged, analgesia, increased cephalad spread and, subsequently, an increased risk of delayed respiratory depression. Lipid-soluble opioids also resemble local anaesthetics in terms of their p*K*a, molecular weight and partition coefficients, which may explain some of the analgesic effects of CSF opioids.

Table 1: Comparison of intrathecal opioid characteristics

Opioid	p*K*a	Octanol/water Partition co-efficient	Intrathecal/intravenous potency ratio	Onset of analgesia (min)	Duration of analgesia (hours)	Clinical dose range
Morphine	7.92	1.4	200–300:1	60–120	18–24	0.1–0.5 mg
Diamorphine	7.6	280	?	<10	10–20	0.2–0.5 mg
Fentanyl	8.4	813	10–20:1	<10	1–4	5–30 µg
Sufentanil	8.02	1778	10–20:1	<10	2–6	2.5–10 µg

Morphine

Morphine is a hydrophilic phenanthrene derivative, which is approximately 100 times less potent than fentanyl when used intravenously. Compared to the lipophilic opioids, morphine has a slow onset (up to 60 minutes) and a significantly longer duration of action (approximately 12–24 hours). Due to its poor lipid solubility (octanol/water partition

coefficient: 1.4), intrathecal morphine is slow to bind to dorsal horn receptors in the spinal cord, and free opioid in the CSF may migrate supraspinally, resulting in delayed respiratory depression.

Fentanyl

Fentanyl, which is highly lipophilic and has an octanol/water partition coefficient of 813, shows a rapid distribution in both receptor and non-receptor binding sites, such as epidural fat, myelin and white matter, resulting in a high volume of distribution in the spinal cord and thus a rapid onset of action. Despite its high lipid solubility, only 8% of the unionised molecule is available for diffusion to receptor sites in the grey matter, due to its relatively high p*K*a value (8.4). Thus, after intrathecal administration, the CSF concentration of fentanyl decreases rapidly, while the epidural and plasma concentrations increase with resultant systemic effects.

Diamorphine

Diamorphine is a purified derivative of heroin (diacetylmorphine). It is a lipid soluble pro-drug that lacks intrinsic opioid activity, but is rapidly metabolised by esterases in the neural tissue and transformed into the water-soluble metabolites 6-monoacetylmorphine and morphine. Diamorphine has higher liposolubility than morphine (octanol/water partition coefficient of 280 vs. 1.4, respectively), which allows it to cross the dura more readily than morphine, thus resulting in rapid onset of action. Although diamorphine has lower lipid solubility than fentanyl, a higher proportion of the drug is available across receptor sites due to its lower p*K*a; it is then metabolised to active metabolites resulting in a longer duration of action. The clinical use of diamorphine is justified by its potential advantages over morphine; its higher liposolubility means that it has a more rapid onset of action and lower effective duration of action, together with a better adverse effects profile but without risk of delayed respiratory depression. Thus, diamorphine combines the advantageous effects of both morphine and fentanyl by the virtue of its physical properties.

Intrathecal opioids and postoperative pain relief

Intrathecal opiate analgesia has been widely used in obstetric, orthopaedic, major abdominal, laparoscopic and spinal surgeries. The analgesic effects of a single injection of intrathecal opioid can last for up to 24 hours. In comparison with epidural analgesia, use of

intrathecal analgesia is associated with early postoperative mobility, and reduced postoperative morbidity, length of hospital stay and costs.

Obstetrics

The use of spinal opioids to control postoperative pain has become established practice in obstetric anaesthesia. The physiochemical properties of diamorphine make it an ideal intraoperative supplement, producing an excellent postoperative analgesic effect after lower segment caesarean section (LSCS). Intrathecal diamorphine for postoperative analgesia after Caesarean section has been shown to prolong the analgesic effect, minimise opioid consumption and improve satisfaction among mothers. While Saravanan et al. established 0.4 mg as the optimal intrathecal dose for LSCS, other studies indicated that the use of up to 1 mg of diamorphine was associated with superior analgesic effects without any worsening of side effects [5–6]. The National Institute for Clinical Excellence (NICE) recommend a diamorphine dose of 0.3–0.4 mg for analgesia after elective Caesarean section [7]. Interestingly some authors have also suggested that obstetric patients could be protected against respiratory depression as a result of their high levels of progesterone, which is a potent respiratory stimulant.

Orthopaedics

Low-dose intrathecal opioids have been shown to provide effective analgesia after hip and knee arthroplasty. The optimal dose for morphine in total hip arthroplasty (THA) was suggested to be 100 µg; this dose provided effective analgesia for up to 21 hours [9]. Recently, a cross-surgical, collaborative European study (PROSPECT) recommended a dose of 0.1 – 0.2 mg of intrathecal morphine after THA, which avoided the need for patient-controlled analgesia (PCA) or monitoring in a high-dependency unit. In patients undergoing knee arthroplasty, higher doses of morphine (of 200–500 µg, in keeping with the greater severity of pain associated with total knee arthroplasty) have been shown to reduce postoperative analgesic requirements [9]. In a randomised controlled trial (RCT), Bowery et al. demonstrated that morphine provided better analgesia at a dose of 0.5 mg compared to 0.2 mg, and with no increase in adverse effects [10]. Intrathecal diamorphine, which is still commonly used in the UK, has not been as extensively employed in arthroplasty patients, but is routinely used at a dose of 0.2–0.5 mg. Intrathecal opioids have also been used in hip fracture surgery. Diamorphine is preferred by anaesthetists in the UK, but there is no clearly optimal dose of diamorphine with respect to the risk/benefit ratio in hip fracture patients. The Association of Anaesthetists of Great Britain and Ireland (AAGBI) recommends that the

use of intrathecal opioids should be restricted to ≤ 25 µg of fentanyl in hip fracture surgery [11].

General surgery and urology

The utility of diamorphine in major abdominal and pelvic surgery is unclear because the analgesic effects wear off after the first 24 hours, necessitating a change to either epidural analgesia or PCA. Khaled et al. examined the safety profile and analgesic efficacy of three different doses of intrathecal morphine (0.2, 0.5 and 1 mg) in patients undergoing major lower abdominal surgery. They concluded that 1 mg of intrathecal morphine provided superior analgesia compared to lower doses, without any significant increase in adverse effects [12]. Similar results have also been noted with the use of intrathecal morphine in patients undergoing radical retropubic prostatectomy [13]. Ultra-low-dose intrathecal morphine (0.05 mg) has been used to control pain due to detrusor muscle spasm after transurethral resection of the prostate (TURP).

Minimally invasive surgery

Spinal analgesia with diamorphine is the most commonly used analgesic technique for major laparoscopic procedures in the UK. Given the nature of the physiological insult and recovery profile following laparoscopic procedures, spinal analgesia with long-acting opioids constitutes a logical option. Spinal analgesia offers intense analgesia in the immediate postoperative period, and permits early mobilisation on the first postoperative day.

In patients undergoing laparoscopic colorectal surgery, there are multiple randomised controlled trials comparing studies comparing epidurals, spinal and patient controlled analgesia. Virlos et al. reported reduced median postoperative pain scores, early mobilisation and reduced length of hospital stay in patients who received intrathecal diamorphine at a dose of 1–1.5 mg plus 10 mg of bupivacaine [14]. Similar results were reported by Levy et al. with the use of 0.25 mg of diamorphine and 15 mg of bupivacaine [15]. Although similar improvements in pain scores were reported by Wongyingsinn et al. with 0.15–2 mg of morphine, they noted no differences in time for mobilisation or length of hospital stay [16]. Intrathecal morphine at a dose of 0.3 mg has also been reported to reduce postoperative pain, systemic opioid consumption and length of hospital stay after laparoscopic bariatric surgery [17].

Despite routine use, there is a lack of evidence regarding the optimum dose of intrathecal opioid for laparoscopic surgery. A recent survey noted wide variability in the dose of

intrathecal diamorphine used (range: 0.1–2 mg) with the majority of individuals receiving < 0.5 mg.

Spine

Administration of intrathecal opioids for spinal surgery has been shown to confer a number of advantages, including decreased intraoperative blood loss, low incidence of pulmonary complications, preservation of gastrointestinal function and high-quality analgesia [18]. Gall et al compared the analgesic effects of two low-dose intrathecal opioid regimes (morphine at 2 and 5 μg kg^{-1}) after spinal fusion in children,and reported no differences in analgesia or the incidence of side effects between the two doses [19]. Eschertzhuber et al. [20] evaluated the effects of intrathecal morphine at two different doses (5 and 15 μg kg^{-1}), combined with a fixed dose of intrathecal sufentanil (1 μg kg^{-1}), in children undergoing elective spinal fusion and reported no significant advantage of administration at the higher dose. However, patients undergoing lumbar spine surgery experienced greater pain relief with 15 g kg^{-1} intrathecal diamorphine compared to 5 μg kg^{-1} or saline alone (as a control), without any increase in adverse effects [21].

Day cases

Fentanyl, the most frequently used intrathecal lipophilic opioid, has been shown to have a rapid onset (10–20 minutes) and short duration of action (4–6 hours), with minimal cephalad spread when administered in single doses of 10–30 μg; thus, it the least likely of all the intrathecal opioids to result in delayed respiratory depression. After a single administration, fentanyl can be used in day case arthroscopic surgery, where it enhances analgesia without prolonging hospital stay. Morphine is unsuitable for day case surgery because of its slow onset time (30–60 minutes), dose-related duration of analgesia (13–33 hours) and unfavourable side effect profile, particularly delayed onset respiratory depression.

Paediatrics

Reports of the use of intrathecal opioids in paediatric cases is limited to children undergoing spinal surgery; its use in other surgeries is limited by concerns over respiratory depression.

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Additives

Local anaesthetics

Local anaesthetics are the most commonly used drugs in conjunction with intrathecal opioids. Intrathecal opioids for arthroplasty and urological procedures are generally used for spinal anaesthesia. The use of opioids in conjunction with local anaesthetics improves the quality of intraoperative analgesia and prolongs the duration of postoperative analgesia. Kumar et al. [22] studied the effects of the addition of fentanyl to intrathecal bupivacaine in patients undergoing urological procedures, and reported that administration of low-dose bupivacaine paus fentanyl was superior with respect to early postoperative recovery, resulting in earlier discharge and better outcomes, and thus benefitting elderly patients with comorbidities. In a meta-analysis of 65 RCTs (including 3,338 patients, 1,932 of whom received opioids), Popping et al. [23] found that the duration of postoperative analgesia was prolonged by morphine (315 to 641 minutes) plus fentanyl (60 to 168 minutes). Morphine decreased the number of patients requiring opioid analgesia after surgery and decreased pain intensity for up to 12 hours postoperatively. In the practice guidelines for acute pain management in the perioperative setting, provided by the American Society of Anesthesiologists (ASA) Task Force on Acute Pain Management, it is stated that “There is an improvement in pain scores when neuraxial morphine is combined with LA compared to neuraxial morphine alone (Category A1 evidence)” [24]. Despite its routine use, insufficient data are available to allow meaningful conclusions to be drawn regarding the efficacy of intrathecal diamorphine.

Clonidine

Clonidine is a centrally acting partial alpha-2 adrenoceptor agonist. In their RCT performed in patients undergoing total knee replacement, Sites et al. found that intrathecal morphine (250 µg) combined with clonidine (25 or 75 µg) provided a superior analgesic effect compared to intrathecal morphine alone. They reported that combined administration of intrathecal clonidine and morphine decreased 24-hour intravenous morphine consumption by 13 mg (P = 0.028) compared to intrathecal morphine alone [25]. However, in a meta-analysis of seven studies, Engelman and Marsala concluded that although addition of intrathecal clonidine to intrathecal morphine prolonged the duration of analgesia, clinical benefits were minimal and the frequency of hypotension was increased [26].

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Ketorolac

Some reports have described the use of a combination of intrathecal morphine and ketorolac (a non-selective COX inhibitor) for postoperative pain control. In patients undergoing knee arthroplasty, Lauretti et al. demonstrated that while either intrathecal morphine (at a dose of 200 mg) or intrathecal ketorolac (at 2 mg) in combination with bupivacaine spinal anaesthesia resulted in a latency of 7–8 hours to the first rescue analgesic, administration of both agents together doubled the latency to rescue analgesic to 15 hours, suggesting an apparent synergistic effect [27].

Adverse effects

The most common side effects of intrathecal opioids are pruritus, nausea and vomiting, delayed gastric emptying and urinary retention. Sedation and respiratory depression are the most serious adverse effects, and are thus of the greatest concern to clinicians. Certain rare side effects, such as bradycardia, persistent hiccups, priapism, resistant hypothermia and nystagmus, have also been reported. The side effects are mediated by opioid receptors. At present, there is no evidence for correlations between opioid dose and adverse effects in the acute pain setting.

Respiratory depression

A recent survey of 270 anaesthesia departments revealed that respiratory depression was the most worrisome adverse effect of intrathecal opioid use [1]. The incidence of respiratory depression varied between 3% and 7% in previous studies. Shapiro et al. studied the records of 1,524 patients treated with morphine between 1999 and 2002, to establish the incidence of respiratory depression (defined as ≤ 10 bpm). They reported an incidence of 0.69% with use of spinal opioids, compared to 1.86% with PCA and 0.59% with epidural opioids [28].

However, most recent European surveys [29–30] have indicated a low incidence of respiratory depression, of between 0.03% and 0.36%, which may be due to the use of lower doses and avoidance of concomitant sedatives and opioids via other routes. This recently reported lower incidence of respiratory depression compares favourably with the rate of 1.2% reported with opioid administration via PCA, and with the rate of 0.9% associated with intramuscular opioids.

Unfortunately, there is no clear definition of the term “respiratory depression” in the literature; some studies used a drop in oxygen saturation, while others used respiratory

rate or some combination of both. However, both drop in oxygen saturation and respiratory rate can be poor measures of respiratory depression during the postoperative period. Measurement of sedation score and timely blood gas analysis may provide a more accurate clinical picture. Prevention is the best treatment for respiratory depression. Table 2 summarises Practice Guidelines by ASA Task force for the Prevention, Detection, and Management of Respiratory Depression Associated with Neuraxial Opioid Administration[31]

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Table 2

Identification of Patients at Increased Risk of Respiratory Depression	**Prevention of Respiratory Depression after Neuraxial Opioid Administration**	**Management and Treatment of Respiratory Depression**
Conduct a focused history and physical examination before administering neuraxial opioids. Direct particular attention toward signs, symptoms, or a history of sleep apnea, co-existing diseases or conditions (e.g., diabetes, obesity), current medications (including preoperative opioids), and adverse effects after opioid administration. A physical examination should include, but is not limited to, baseline vital signs, airway, heart, lung, and cognitive function.	Monitoring for Respiratory Depression Monitor all patients receiving neuraxial opioids for adequacy of ventilation (e.g., respiratory rate, depth of respiration [assessed without disturbing a sleeping patient]), oxygenation (e.g., pulse oximetry when appropriate), and level of consciousness. Increased monitoring (e.g., intensity, duration, or additional methods of monitoring) may be warranted for patients at increased risk of respiratory depression (e.g., unstable medical condition, obesity, obstructive sleep apnea, concomitant administration of opioid analgesics or hypnotics by other routes, extremes of age).	For patients receiving neuraxial opioids, supplemental oxygen should be available. Administer supplemental oxygen to patients with altered level of consciousness, respiratory depression, or hypoxemia and continue until the patient is alert and no respiratory depression or hypoxemia is present. Maintain intravenous access if recurring respiratory depression occurs. Reversal agents should be available for administration to all patients experiencing significant respiratory depression after neuraxial opioid administration. In the presence of severe respiratory depression, initiate appropriate resuscitation. Noninvasive positive pressure ventilation may be considered for improving ventilatory status. If frequent or severe airway obstruction or hypoxemia occurs during postoperative monitoring, initiate NIV

This document also provides specific guidance for timing and duration of monitoring based on the type, dose and combinations of drugs.

Pruritus

Although pruritus is one of the most common side effects of intrathecal opioids, the incidence is unrelated to the dose and ranges between 0% and 100%. Pruritus is reported most frequently in obstetric cases, wherein gestational hormones may cause alterations in the opioid receptor population. Pruritus predominantly affects the face and upper body, and is believed to be mediated by the interaction between the drug and mu opioid and 5-HT3 receptors in and around the trigeminal nucleus. This interaction stimulates the substantia gelatinosa of the dorsal horn, initiating the itch reflex. Ondansetron (a 5-HT3 antagonist) has been shown to reduce the incidence of opioid-induced pruritus in obstetric populations. There is no association between histamine release and opioid-induced pruritus, and therefore there is no benefit of using antihistamines.

Low-dose propofol has been shown to be of some benefit, but the potential sedation associated with its administration makes its use in postoperative wards impractical. Low-dose opioid receptor antagonists, such as naloxone and naltrexone, have been shown to be of benefit in opioid-induced pruritus, without reversing analgesia. However, further studies are required to establish the optimum dose.

Nausea and vomiting

Intrathecal opioid use is commonly associated with post-operative nausea and vomiting (PONV). The incidence of PONV was reported to be particularly high in female patients and obstetric populations. The reported incidence of PONV after intrathecal opioid varies between 22% and 67% [32], and is thought to be mediated by cephalad migration of the opioid to the chemoreceptor trigger zone, where the opioids can act as partial dopamine-2 receptor agonists. The aetiology and management of opioid-induced PONV will not be discussed further herein, as it has been covered extensively in multiple reports on anaesthesia.

Urinary retention

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Urinary retention is considered one of the most distressing non-respiratory adverse effects associated with the use of intrathecal opioids, and is more common in men than women. A prospective RCT to establish the dose–response relationship between intrathecal morphine and incidence of adverse effects reported an incidence of urinary retention of 20%–40% at 2 hours after morphine injection, which decreased to 10% after 24 hours [33]. However, this study was limited by the small number of cases, and by the patients being in receipt of morphine injections for chronic back pain. Therefore, it is imperative to monitor bladder function either clinically or by ultrasound and, when considered appropriate, to install a urinary catheter aseptically in the operation theatre at the end of the surgery, especially in high-risk patients.

Neurotoxicity

There is no evidence from either human or animal studies of deleterious effects in the spinal cord arising from single, multiple or continuous injection of commonly used opioids.

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