Adjuvant analgesics in spinal surgery

ABSTRACT

Peri- and postoperative pain control can present a challenge to any doctor, particularly in the setting of spinal surgery. The use of adjuvant pain agents and multimodal analgesia is changing the face of modern anaesthesia and offering clinicians more avenues to control perioperative pain. This article discusses the use of adjuvant medications and some of the evidence surrounding their use in spinal surgery.

Patients presenting with chronic pain for surgical intervention can present a challenge with regard to postoperative pain management. Spinal surgery has high levels of postoperative pain compared to other procedures (Devin and McGirt, 2015). Many patients presenting for spinal surgery will already be taking regular opioid analgesia, making postoperative pain control difficult (Dunn et al, 2016).

The World Health Organization recommends the addition of adjuvant medication in control of all kinds of pain (Vargas-Schaffer, 2010). Adjuvant medication including antidepressants, anticonvulsants, N-methyl-D-aspartate (NMDA) receptor antagonists, membrane stabilizers and α agonists has been used to modulate pain and reduce postoperative opioid use (Dunn et al, 2016). The American Society for Anesthesiologists recommends multimodal pain management therapy where possible (American Society of Anesthesiologists Task Force on Acute Pain Management, 2012).

This article discusses the use of alternative pain medications and suggests some alternative pain management options for those with chronic pain undergoing spinal procedures.

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NMDA receptor antagonists

Ketamine is a non-competitive NMDA receptor antagonist that acts on receptors in both the central and peripheral nervous systems (Nielsen et al, 2017). It may also have a role in reducing or reversing opioid tolerance (Himmelseher and Durieux, 2005; Devin and McGirt, 2015).

A recent trial (Nielsen et al, 2017) demonstrated significantly less use of opioids in the first 24 hours post-spinal surgery when ketamine was given as a bolus followed by an infusion intraoperatively. These findings mirrored those of an earlier study (Loftus et al, 2010) which looked at postoperative pain and analgesia consumption in those with chronic pain undergoing spinal surgery. Intraoperative ketamine in these patients reduced opiate consumption by 37%, and this benefit was also seen at 6 weeks postoperatively (Loftus et al, 2010).

The American Pain Society suggests a 0.5 mg/kg bolus dose of ketamine for surgery followed by an intraoperative infusion of 10 μg/kg/min with or without a low dose postoperative infusion (Chou et al, 2016).

Magnesium is also an NMDA receptor antagonist. It works in a non-competitive fashion to block extracellular calcium movement into the cell and decreases central sensitization (Guo et al, 2015). It has also been shown to reduce the requirements for opioids intraoperatively and postoperatively (Oguzhan et al, 2008) for patients undergoing lumbar disc surgery. In a review article by Guo et al (2015), magnesium was found to have good efficacy in reducing postoperative pain, significantly so in those undergoing orthopaedic surgery.

Lidocaine

Lidocaine is a local anaesthetic agent with anti-inflammatory, analgesic and antihyperalgesic properties (Daykin, 2017). These effects are thought to be mediated by the inhibition of sodium channels and disruption of neural transmission at the site of injury. It is also thought to cause suppression of peripheral and central sensitization (Daykin, 2017).

Lidocaine is effective in reducing opiate requirements and improving recovery after bowel surgery (Ventham et al, 2015). It is also a useful analgesic agent in elderly patients undergoing bowel and urological surgery as well as providing benefit for those with opioid-refractory pain from critical ischaemic limb, malignancy and neuropathic pain (Daykin, 2017).

Farag et al (2013) found that a lidocaine infusion in patients undergoing multilevel spinal surgery improved postoperative pain scores, but it did not reduce opioid

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consumption. In a similar trial, Kim et al (2014) showed a significant reduction in pain scores and use of fentanyl with lidocaine bolus and intraoperative infusion.

A recent prospective study on patients undergoing multiple level spinal arthrodesis found that intraoperative lidocaine infusion failed to accelerate postoperative recovery and shorten length of stay (Dewinter et al, 2017). This study used a bolus and infusion of lidocaine intra- and postoperatively. The authors proposed several reasons for this divergence including the use of intraoperative opiates possibly masking beneficial effects as well as more extensive spinal surgery being performed in this particular group of patients (Dewinter et al, 2017).

Use of a bolus dose of lidocaine up to 2 mg/kg is recommended followed by an infusion of 1–3 mg/kg/hr (Ramaswamy et al, 2013, Ventham et al, 2015). However, there is no clear consensus on duration of infusion and whether this should continue into the postoperative period (Chou et al, 2016).

Alpha-2 agonists

Clonidine is an α2-adrenoceptor agonist that can be used as an additive to peripheral and central nerve blockade as well as parenterally as part of multimodal analgesia. It stimulates α2 adrenergic receptors in the brainstem which then activate inhibitory neurones and reduce CNS sympathetic outflow (Nguyen et al, 2017). Peripherally, it blocks C fibres and may interact with inhibitory G proteins to reduce pain (Turan et al, 2016).

A large study conducted as a subgroup analysis of the POISE-2 trial (Turan et al, 2016) found that clonidine did not reduce opioid consumption in comparison to placebo; it also found no reduction in pain scores. A meta-analysis (Blaudszun et al, 2012) found that clonidine reduced morphine consumption by approximately 25% at 24 hours. However, there were differences in the routes of administration and dosages used between the POISE 2 subgroup and the studies included in the meta-analysis, making it difficult to draw direct comparison.

Side effects can preclude the use of α2 agonists. Haemodynamic compromise can occur with use of clonidine and this should be considered when choosing it as an analgesic agent. An intravenous dose of 2–5 μg/kg is recommended (Kaye et al, 2017).

Dexmedetomidine is a highly selective α2-adrenoceptor agonist (Nguyen et al, 2017). Intraoperatively, it has been shown to decrease opioid requirements (Nguyen et al, 2017) and may cause less haemodynamic compromise as a side effect (Turan et al, 2016). In spinal surgery, it reduces opioid requirements and increases the pain-free period (Dunn et al, 2016).

Neuropathic pain medications

Pregabalin and gabapentin are both gabapentinoids that exert their effect by reducing the number of voltage-gated calcium channels trafficked to the cell membrane, thereby reducing release of neurotransmitters into the nerve synapse (Helander et al, 2017). Both gabapentin and pregabalin have shown efficacy in the postoperative period in reducing opioid consumption (Helander et al, 2017). The American Pain Society recommends their use in the perioperative period for analgesia (Chou et al, 2016).

Doses as low as 300 mg of gabapentin are effective in reducing opiate consumption and postoperative pain in spinal surgery (Dunn et al, 2016). Pregabalin doses of 150 mg also significantly reduced postoperative opioid consumption (Gritsenko et al, 2014). Reduction of chronic postoperative pain secondary to the use of gabapentinoids has not been ambiguous (Reddi, 2016). Gabapentin has been found to be similar to placebo in the prevention of chronic post-surgical pain, but pregabalin may be superior to placebo in this role (Clarke et al, 2015).

Gabapentinoids are generally well tolerated, although side effects include dizziness, sedation and visual disturbances (Schmidt et al, 2013).

Amitriptyline is a tricyclic antidepressant which is also used in the management of neuropathic pain. It works through preventing reuptake of noradrenaline and serotonin (Maizels and McCarberg, 2005). It has proven efficacy in post-herpetic neuralgia, diabetic neuropathy and central pain syndromes (Kremer et al, 2016) at doses lower than those required for treatment of clinical depression.

Tricyclic antidepressants in the management of chronic neuropathic pain have been extensively researched in the past 20 years. Those tricyclic antidepressants that prevent noradrenaline re-uptake appear to have a mild to moderate reduction in the symptoms of chronic low back pain (Müller-Schwefe et al, 2017). The recommended initial dosage is 10–25 mg at night (Tumber, 2014). The possibility of their use for perioperative analgesia has yet to be fully researched.

Dexamethasone

Dexamethasone acts by reducing the expression of pro-inflammatory genes (Helander et al, 2017) thereby reducing tissue inflammation. Its effects in reducing postoperative nausea and vomiting are well studied.

A systematic review in published in 2013 found that a single perioperative dose of dexamethasone 0.1 mg/kg was significantly associated with reduced opioid consumption, reduced need for rescue analgesia and reduced postoperative pain (Waldron et al, 2013). This supported the results of an earlier meta-analysis (De Oliveira et al, 2011). Some authors have suggested that a second dose may be useful to further reduce postoperative pain follow joint arthroplasty (Bruhn et al, 2017).

Nielsen et al (2015) demonstrated a reduction in pain scores during mobilization with high dose dexamethasone following lumbar discectomy. Bednar et al (2015) investigated changes in opioid consumption, length of stay and wound infections following institution of dexamethasone co-analgesia as standard practice in spinal

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> [Opioids] can be administered in a variety of different routes for postoperative analgesia; oral administration is preferred over parenteral administration where possible.

fusion and discectomy. The authors found no difference in terms of side effects and morphine consumption but did find a 25% reduction in length of stay (Bednar et al, 2015).

Concerns regarding wound healing and infection rates have been allayed by several studies (Nielsen et al, 2015; Helander et al, 2017). Single dose dexamethasone has been associated with raised blood glucose levels postoperatively, but it is unclear if this has significant effects (Helander et al, 2017). Caution is advised in administration of glucocorticoids to diabetic patients (Helander et al, 2017).

Opioids

Opioids bind G-protein coupled opioid receptors with differing affinity in the CNS. They can be administered in a variety of different routes for postoperative analgesia; oral administration is preferred over parenteral administration where possible (Chou et al, 2016).

Neuraxial opioids have demonstrated superior efficacy in meta-analyses over parenteral opioid administration (Helander et al, 2017). There is a significant body of evidence suggesting improved postoperative analgesia (Dunn et al, 2016). A recent trial demonstrated efficacy of intrathecal opioids and oral analgesia without a need for intravenous oxycodone or epidural infusion following posterior spinal fusion in teenagers with scoliosis (Li et al, 2017). This approach reduced pain scores, reduced the need for routine postoperative admission to intensive care and reduced length of hospital stay (Li et al, 2017).

Parenteral opioids offer rapid onset of analgesia and reliable bioavailability (Helander et al, 2017). Parenteral oxycodone has higher efficacy than morphine with a more favourable side-effect profile (Helander et al, 2017). A recent narrative review of trials relating to postoperative use of oral oxycodone found that it had comparable or better pain relief than morphine following laparoscopic surgery, obstetric surgery and spinal surgery (Cheung et al, 2017).

Pethidine is a μ-receptor opioid agonist that has active metabolites (Camu and Vanlersberghe, 2002). It is commonly used to relieve postoperative shivering and may have a more favourable side-effect profile in terms of postoperative nausea and vomiting in comparison to morphine after spinal surgery (Wu et al, 2011).

Non-steroidal anti-inflammatory drugs and paracetamol

Non-steroidal anti-inflammatory drugs reduce pain through reduction of inflammatory mediators (Gupta and Bah, 2016). Paracetamol's mechanism of action is less certain (Helander et al, 2017).

The use of paracetamol and non-steroidal anti-inflammatory drugs perioperatively improves pain scores and reduces opioid consumption (Dunn et al, 2016) compared to opioid analgesia alone. Paracetamol (Helander et al, 2017) is more effective than placebo in reducing opioid consumption. It is unclear whether there is a benefit of intravenous over oral administration (Helander et al, 2017). Non-steroidal anti-inflammatory drugs provide significant pain relief post-spinal surgery and also reduce postoperative morphine consumption (Dunn et al, 2016).

The American Pain Society recommends regular combination therapy with both non-steroidal anti-inflammatory drugs and paracetamol for postoperative pain (Chou et al, 2016) when not contraindicated. They cite the different mechanisms of action as having an additive effect both with or without the use of opioids (Chou et al, 2016).

It has been suggested that non-steroidal anti-inflammatory drugs may contribute to non-union or mal-union of fractures, but a meta-analysis in 2010 (Dodwell et al, 2010) found no statistically significant association between the two. They are contraindicated in those with renal impairment (Kaye et al, 2017), and relatively contraindicated in those with gastric ulceration and congestive heart failure.

Conclusions

This article has discussed some alternative analgesic options for use in those undergoing spinal surgery. The authors recommend that the use of non-opioid adjuvant analgesics be considered as an extra armament in the management of both intraoperative and postoperative pain for patients undergoing complicated spinal surgery. **BJHM**

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KEY POINTS

- Spinal surgery can present a number of challenges for perioperative pain management, particularly in patients with chronic pain.
- Adjuvant analgesics have demonstrated good efficacy in control of all kinds of postoperative pain.
- N-methyl-D-aspartate (NMDA) receptor antagonists and neuropathic pain medications can reduce opioid requirements perioperatively in spinal surgery.
- Other adjuvant medications warrant further research as to their optimum dose and duration of treatment in the realm of spinal surgery.
- While opioids have been the mainstay of perioperative analgesia, alternative agents offer safe and effective additional treatment options.

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