

Non-opioid-based adjuvant analgesia in perioperative care



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Key points

Perioperative pain can result in hyperalgesia, central sensitization, and ultimately chronic postsurgical pain.

Multimodal analgesia may improve pain management, decrease opioid requirement and possibly opioid-related side-effects.

Atypical analgesics, more often used in chronic pain, are increasingly used as for acute pain control.

Ketamine, pregabalin, gabapentin, i.v. lidocaine, and α_2 agonists have some evidence of efficacy in the perioperative setting.

The risk–benefits of these adjuvant drugs should be carefully considered in each case.

Introduction

Opioids are the mainstay of perioperative analgesia but can have several well-known dose-related side-effects.¹ More recently, there have been concerns that large doses of opioids may cause acute tolerance and hyperalgesia, resulting in worsening pain control.¹ Various drugs and techniques have been used as part of multimodal analgesia with the aim of improving pain management and decreasing opioid consumption and opioid-related side-effects.¹ Of these, the benefits of paracetamol, non-steroidal anti-inflammatory agents, and regional anaesthesia techniques are well established and hence will not be discussed further in this review.

Acute perioperative pain can produce structural and functional changes in the pain pathway, resulting in hyperalgesia and central sensitization.¹ Increasingly the problem of acute perioperative neuropathic pain is being recognized.¹ Poorly controlled pain at the time of surgery predisposes to chronic postsurgical pain (CPSP).¹ Because of this, drugs traditionally used for chronic neuropathic pain are being used more commonly in the perioperative period. This includes drugs such as antidepressants (e.g. amitriptyline), anticonvulsants (e.g. gabapentinoids), *N*-methyl-D-aspartate (NMDA) receptor antagonists (e.g. ketamine, magnesium), membrane stabilizers (e.g. lidocaine), and α_2 agonists (e.g. clonidine and dexmedetomidine). Current evidence does not support the use of antidepressants and magnesium for perioperative pain or preventing CPSP.^{1,2} Only ketamine, the gabapentinoids (pregabalin and gabapentin), α_2 agonists, and i.v. lidocaine have some evidence for perioperative use.¹ This review will focus on these five drugs. Their mechanism of action, current evidence for use in perioperative settings, opioid-sparing effect, side-effects, tolerability, and their role as preventive analgesia

(preventing CPSP) will be discussed. While interpreting the efficacy of an analgesic in a multimodal setting, we caution our readers when assessing the importance of reduced analgesic consumption if that has not resulted in achieving similar pain scores.

In this review we have excluded the evidence for some of these drugs used neuraxially and as part of regional blocks. We have used the National Health and Medical Research Council (NHMRC) levels of evidence (Appendix) wherever available to describe the level of evidence.

Ketamine (NMDA receptor antagonist)

Role of NMDA receptors in nociception

Nociceptive stimuli cause glutamate release from excitatory synapses. This in turn activates the NMDA receptors in the central and peripheral nervous system, resulting in the voltage-dependent flow of Na^+ and Ca^{2+} ions into the cell and K^+ out of the cell. NMDA receptor activation has a key role in the development of central sensitization, wind up, and pain memory resulting in a pathological pain state. This is manifested clinically as hyperalgesia and allodynia. Chronic opioid consumption also produces changes in the nervous system similar to that seen with central sensitization. They activate the μ -receptors which can increase the effectiveness of glutaminergic synapses at the level of NMDA receptors, resulting in the opioid-induced hyperalgesia (OIH).

Mechanism of clinical effect

Ketamine in subanaesthetic doses non-competitively blocks the NMDA receptors. They also modify these receptors via allosteric mechanisms. It has 'antihyperalgesic', 'antiallodynic',

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and ‘antitolerance’ effects. Based on its mechanism of action, we expect ketamine to be a useful adjuvant in managing pain attributable to central sensitization such as in severe acute pain, neuropathic pain, and OIH. By preventing hyperalgesia, sensitization, and wind up, it may also reduce the incidence of CPSP.¹

Role in acute perioperative pain

Ketamine has been widely used as an adjuvant analgesic in a variety of perioperative pain settings.^{3,4} Reductions of up to 20–25% in pain intensity and 30–50% in analgesic consumption up to 48 h after surgery have been reported (Level I).^{3,4} An associated reduction in opioid-related adverse effects such as decreased PONV was found.^{3,5} The analgesic effect of ketamine was independent of the type of opioid used, timing of ketamine administration, and dose of ketamine.⁵ Major side-effects are uncommon and include psychomimetic effects such as hallucinations, nightmares, sedation, nausea, and vomiting.² The psychomimetic effects were more common in patients undergoing awake procedures than after procedures under general anaesthetic (Level I).⁴ The actual degree and significance of the benefits of ketamine in individual patients will depend on the extent of anticipated pain intensity, opioid consumption, nature of surgery and the nature of alternative analgesia. The evidence for the benefit of ketamine in various clinical settings is summarized in Tables 1 and 2. Although promising, based on these data, we cannot recommend ketamine as a routine perioperative analgesic.¹ The concept of pre-emptive analgesia based on the prevention of central sensitization is sound in theory. But some people feel ketamine may be more effective after the NMDA receptors are opened by the nociceptive stimulation. Neither pre-incisional, nor post-incisional, nor the length of administration of ketamine was associated with better outcome. Doses >30 mg in 24 h have not resulted in improved analgesia.³ Because of the heterogeneity in different RCTs and based on results of existing reviews, we cannot recommend a specific administration regimen.

Role in preventive analgesia

McCartney *et al.*² found that 14 of the 24 studies (58%) included in their review, looking at perioperative ketamine via different

routes, resulted in improved analgesia lasting beyond its clinical duration of action. Currently, we have sufficient evidence to suggest that ketamine has preventive but not pre-emptive analgesic effects (Level I).¹

Several RCTs have looked at the role of ketamine in preventing CPSP after different surgeries. Studies including laparotomy, thoracotomy, and hip arthroplasty gave positive results, whereas those involving amputation, knee arthroplasty, thoracotomy, radical prostatectomy, and hysterectomy gave negative results.¹ We need more concrete evidence before we can ascertain the role of ketamine in modulating the development of CPSP.

Gabapentinoids

The two clinically used gabapentinoids are gabapentin and pregabalin. Although they are currently only licensed for chronic neuropathic pain, epilepsy, and anxiety (pregabalin only), they are increasingly used as an adjuvant for perioperative analgesia. Compared with gabapentin, pregabalin has greater analgesic potency (two to three times more potent) and a more favourable pharmacokinetic profile (more rapidly absorbed, better and predictable oral bioavailability, and longer acting).

Mechanism of clinical effect

Gabapentinoids mainly act on the α -2- δ -1 subunit of pre-synaptic calcium channels and inhibit neuronal calcium influx. This results in a reduction in the release of excitatory neurotransmitters such as glutamate, substance P, and calcitonin gene-related peptide from primary afferent nerve fibres thus suppressing neuronal excitability after nerve or tissue injury. They may prevent central sensitization and subsequent hyperalgesia and allodynia, with only minor effects on normal nociceptive pathways. Gabapentinoids, as part of multimodal analgesia, may contribute to better postoperative pain management, enhance opioid analgesia, prevent opioid tolerance, and prevent CPSP. They also have anxiolytic and sleep-modulating properties, making them useful adjuvants in perioperative care. Based on their proposed mechanism of action, they are unlikely to be of any benefit as sole agents for the management of acute perioperative pain.⁶

Table 1 Current evidence for use in perioperative pain and prevention of CPSP

Drug	Acute perioperative pain			Prevention of CPSP	Side-effects
	Pain intensity	Analgesia/opioid consumption	Opioid-related side-effects		
Ketamine	Decreased (20–25%; Level I)	Decreased (30–35%; Level I)	Decreased (Level I)	Inconsistent (Level II)	Psychomimetic—hallucination, dreams
Pregabalin	Decreased but inconsistent (Level I)	Decreased (Level I)	Decreased but inconsistent (Level I)	Yes (Level I)	Visual disturbance, dizziness
Gabapentin	Decreased	Decreased (20–62%; Level I)	Decreased (Level I)	Yes (Level I)	Dizziness, sedation
I.V. lidocaine	Decreased (Level I)	Decreased (Level I)	Decreased (Level I)	Possibly (Level II)	None but needs caution
Systemic α 2 agonist	Decreased (Level I)	Decreased (Level I)	Decreased (Level I)	No data	Hypotension, bradycardia

Table 2 Summary of clinical benefits

Drug	Summary of clinical benefits
Ketamine	<ul style="list-style-type: none"> Useful adjuvant in painful procedures: upper abdominal, thoracic, and major orthopaedic surgeries (Level I)⁵ Useful adjuvant to PCA analgesia (Level I)¹ Patients with chronic pain issues and on high-dose opioids—decreases pain intensity and opioid consumption lasting much beyond the perioperative period (Level II)¹⁷ Opioid-resistant pain—rescue analgesia (mixed evidence; Level II)¹ Has preventive but not pre-emptive analgesic effect (Level I). Studies looking at the role of ketamine in preventing CPSP have shown only mixed effects (Level II)¹
Pregabalin	<ul style="list-style-type: none"> Risk—benefits probably more acceptable for painful procedures resulting in acute neuropathic pain, requiring large doses of opioids (e.g. cardiothoracic surgery, arthroplasty, or spine surgery) in order for the reduction in opioid-related side-effects to outweigh the side-effects. The evidence for this is limited and needs further research. Risks for minor, laparoscopic, or day-care procedures probably outweigh the benefits⁷ Useful preventive analgesic effect⁹
Gabapentin	<ul style="list-style-type: none"> Benefits similar to pregabalin, but being an older drug has more literature evidence Improved analgesia at rest and movement (Level I) Improved functional recovery with better range of movements and pulmonary function (Level II)¹⁰ Analgesic effect comparable and synergetic with NSAIDs and superior to tramadol¹⁰ Useful adjuvant to epidural analgesia—decreased pain scores, epidural analgesic consumption, and patient satisfaction despite an increase in dizziness¹ In established acute postoperative pain, single-dose gabapentin is superior to placebo but worse than other commonly used analgesic. The NNT was 11 (Cochrane review)¹⁸ Useful preventive analgesic effect⁹ A small RCT (60 patients undergoing abdominal hysterectomy) showed gabapentin was superior to ketamine in preventing CPSP⁹
I.V. lidocaine	<ul style="list-style-type: none"> Useful in visceral pain and improves postoperative bowel function after abdominal surgery—reduces pain and opioid requirements, nausea, vomiting, duration of ileus, resulting in decreased time to pass flatus, faeces and earlier intake of enteral food, rehabilitation, and discharge (Level I)^{12,13} Benefit seen even in patients undergoing laparoscopic colectomy as part of acute rehabilitation programme^{12,13} No proven use in non-abdominal surgeries¹² Probably has a preventive effect after major abdominal and breast surgery (Level II)^{14,15}
Systemic $\alpha 2$ agonist	<ul style="list-style-type: none"> Moderate analgesic benefit—probably better than paracetamol but less than that of ketamine and NSAIDs as inferred from non-systematic indirect comparison¹⁶ All these beneficial effects may come at a price of significant hypotension and bradycardia¹⁹ Useful adjuvant in perioperative care in adults and children because of several useful extra analgesic benefits such as sedation, anxiolysis, analgesia, postoperative shivering, PONV, agitation, mitigation of stress response to surgery and tracheal intubation, anaesthetic-sparing effect, and as supplement to neuraxial and peripheral nerve blocks¹⁶ Decreased perioperative mortality and myocardial infarction especially in high-risk vascular surgeries¹⁹ No evidence for preventive analgesia¹⁶

Pregabalin

Role in acute perioperative pain

Pregabalin is the newer of the two gabapentinoids and has been used in perioperative care over only the last 10 yr. Its role in perioperative pain has been studied in a wide variety of surgical procedures, including orthopaedic, dental, thyroid, gynaecological, laparoscopic, gastrointestinal, and ambulatory surgeries. These studies showed considerable heterogeneity in reporting the dose and duration of treatment and outcome measures such as pain intensity, opioid/analgesic requirements, and side-effects attributable to pregabalin and opioids. This can make drawing useful conclusions difficult.

Two recent reviews looked at the perioperative use of pregabalin. Zhang *et al.*⁷ showed significantly decreased opioid consumption and vomiting but not decreased pain intensity. Engelman and Cateley⁸ reported decreased pain intensity (at rest and movement) and opioid consumption but not decreased PONV. Engelman and Cateley's review is more recent and included 10 of the RCTs included by Zhang *et al.* and 6 more recent RCTs. This could

explain the difference in results. Common side-effects noted include dizziness, sedation, somnolence, vomiting, and visual disturbance. Zhang *et al.*⁷ gave an NNT PONV as 18 and NNH for visual disturbance as 6. Side-effects such as sedation and vomiting may prevent them from taking more opioids and may cause PONV. These side-effects are more troublesome after less painful surgeries, ambulatory surgeries, or both. The majority of the negative studies have been on these groups of patients. The use of pregabalin in various clinical settings is summarized in Table 2.

We should be careful in using pregabalin in elderly and in patients with impaired renal function. We cannot recommend a specific dose and duration of treatment, as this was too variable in different studies. Engelman *et al.* reported that 225–300 mg was the lowest effective dose and both 300 and 600 mg produced identical results.⁸

Role in preventive analgesia

Very few published RCTs have looked at the role of pregabalin in the prevention of CPSP. A recent review and meta-analysis

including three RCTs on patients undergoing lumbar discectomy, knee arthroplasty, and cardiac surgery suggested that pregabalin may have a promising role in preventing the development of CPSP and improving postsurgical function.⁹

Gabapentin

Role in acute perioperative pain

Perioperative gabapentin has been shown to improve analgesia at rest and with movement (Level I).^{1,6,10} Single preoperative dose of gabapentin resulted in a decrease in perioperative opioid consumption by 20–62% [up to 30 (4) mg of morphine equivalents] during the first 24 h (Level I).⁶

Various meta-analyses also reported a decrease in opioid-related side-effects such as nausea (NNT 25), vomiting (NNT 6), urinary retention (NNT 7), and pruritus (NNT 15).⁶ The main side-effect reported with gabapentin was sedation (NNH 35) and dizziness (NNH 12).⁶

The use of gabapentin in various clinical settings is summarized in Table 2.

The degree of benefit was not related to the dose of gabapentin, although one RCT on lumbar discectomy showed an analgesic ceiling effect at 600 mg.¹⁰ The timing (pre- vs post-incision) and use of multiple dose regimens have not been shown to have an impact on the outcome.¹⁰ The dose, timing, and duration of gabapentin in different studies have been very variable and hence we cannot recommend a particular regimen.

Role in preventive analgesia

Gabapentin has had mixed effect in preventing CPSP in different surgical settings. Four of the eight studies included in a recent systematic review showed a positive effect and the meta-analysis demonstrated a moderate-to-large reduction in the development of CPSP.⁹

I.V. lidocaine

Lidocaine is a local anaesthetic most commonly used in infiltration and for central neuraxial and peripheral nerve blocks. Intravenously, it has been used to treat arrhythmias, chronic neuropathic pain, and Bier's block. According to the Cochrane review lidocaine is at least as good as other antineuropathic pain drugs for the treatment of chronic neuropathic pain and is not associated with significant side-effects.¹¹

I.V. lidocaine follows multicompartment kinetics. Steady-state concentrations are reached after 3–4 h of infusion in normal subjects.¹² The concentration of free lidocaine after a given dose will depend on the patient's plasma protein concentration and acid–base status. This results in both intersubject and intrasubject variability in pharmacokinetics and toxic effects. This makes dosing recommendations a problem. Also lidocaine is metabolized to active metabolites by the liver, which is limited by liver perfusion.

Heart failure or drugs that alter hepatic blood flow can therefore significantly affect its clearance.

Mechanism of clinical effect

Lidocaine has analgesic, anti-inflammatory, and anti-hyperalgesic properties. Analgesic effects are thought to be mediated by the suppression of spontaneous impulses generated from injured nerve fibres and the proximal dorsal root ganglion. This occurs by the inhibition of Na channels, NMDA, and G-protein-coupled receptors. The anti-inflammatory effects are attributable to the blockade of neural transmission at the site of tissue injury, resulting in the attenuation of neurogenic inflammation, and to the intrinsic anti-inflammatory property. It inhibits the migration of granulocytes and release of lysosomal enzymes and consequently leads to decreased release of pro- and anti-inflammatory cytokines. This results in the suppression of peripheral and central sensitization, resulting in its proposed anti-hyperalgesic effect.¹²

Role in acute perioperative pain

The current evidence for using i.v. lidocaine for perioperative pain is based on several small RCTs contributing to three recent systematic reviews.^{1,12,13} I.V. lidocaine has been used in various surgeries, including open and laparoscopic abdominal surgeries, tonsillectomy, orthopaedic, cardiac, and ambulatory surgeries. But it has been found to be useful only in abdominal surgery, where anaesthetic and opioid requirements were significantly reduced in the intraoperative period. Several studies have reported a decrease in pain intensity (pain at rest, cough, and movement), opioid requirements, and opioid-related side-effects such as PONV. It decreased the duration of postoperative ileus probably attributable to a combination of opioid-sparing effect, anti-inflammatory actions, decreased sympathetic tone and its direct effect on intestinal smooth muscles.^{12,13} Despite these benefits they have not expedited discharge from PACU and hence have not had a positive effect on ambulatory surgeries.^{12,13} The use of i.v. lidocaine in various clinical settings is summarized in Table 2.

Although there is no clear consensus on the dosage regimen, many studies have used a bolus dose of 100 mg or 1.5–2 mg kg⁻¹ at least half an hour before surgical incision, followed by an infusion of 1.33–3 mg kg⁻¹ h⁻¹ intraoperatively and continued after operation variably up to 24 h.¹² Some of the benefits of lidocaine, similar to leucocyte inhibition, are time dependent. So it may be beneficial to continue the infusion after operation for up to 24 h. These regimens have achieved plasma concentrations between 2 and 5 µg ml⁻¹, although adequate plasma concentrations did not always correlate with analgesic effect.¹² Although none of the studies have reported any major complications, they were not specifically powered to detect them. Hence the safety of i.v. lidocaine in perioperative setting needs to be established in subsequent studies.¹³

Role in preventive analgesia

In many studies, analgesic effect has persisted after the lidocaine infusion was discontinued, which suggests a prevention of central hypersensitivity, peripheral hypersensitivity, or both. Inhibition of NMDA receptors, polymorphonuclear leucocyte priming, or both may play a role in this effect.^{12,14} Perioperative lidocaine was also found to have a preventive effect on postoperative pain for up to 72 h after abdominal surgery.¹¹ A recent RCT on 36 patients undergoing breast cancer surgery showed that perioperative i.v. lidocaine was associated with decreased incidence and severity of persistent pain after breast surgery.¹⁵

α_2 Adrenoceptor agonists

Role of α_2 agonist in pain pathways

α_2 Adrenergic receptors are present in both presynaptic and postsynaptic neurons in the central and peripheral nervous system. Activation of presynaptic receptors results in the propagation of negative feedback loop inhibiting the release of norepinephrine. Activation of postsynaptic receptors in the central nervous system inhibits sympathetic activity.

At supraspinal level, α_2 adrenoceptors are present in high concentrations at the locus coeruleus in the brainstem. It is the origin of the medullospinal noradrenergic pathway, known to be an important modulator of nociceptive neurotransmission. At the spinal level, stimulation of α_2 receptors in the substantia gelatinosa in the dorsal horn results in the inhibition of nociceptive neurons and in the release of substance P.

Mechanism of clinical effect

Clonidine and dexmedetomidine are two commonly used drugs in this class. They activate the G1-protein-gated K channels in the neurons, resulting in membrane hyperpolarization. They also reduce calcium conductance into cells via G0-protein-coupled N-type voltage-gated calcium channels. Because of these effects, they not only prevent neuronal firing but also prevent the local signal propagation. Thus, α_2 adrenoceptor agonists act at supraspinal, spinal, and peripheral sites. Intrathecal or epidural α_2 agonists are useful adjuvants both in postoperative pain setting and in neuropathic and cancer pain setting resulting in longer duration of block.¹⁶

Role in acute perioperative pain

A recent systematic review showed that systemic clonidine and dexmedetomidine were associated with a moderate decrease in pain intensity, opioid consumption, and early postoperative nausea (NNT approximately 9). They were not associated with prolonged recovery time. Other opioid-sparing effects such as respiratory depression, delirium, and effect on immune system were not reported. Clonidine was associated with increased intraoperative (NNH 9)

and postoperative (NNH 20) hypotension and dexmedetomidine was associated with increased incidence of bradycardia (NNH 3).¹⁶ Currently, POISE-2 trial, a large multicentre trial involving 10 000 patients, is looking into the short-term and long-term outcome and safety after perioperative clonidine (<http://clinicaltrials.gov/ct2/show/NCT01082874>). The clinical uses of α_2 agonists are summarized in Table 2.

Comparing clonidine with dexmedetomidine, dexmedetomidine is approximately eight times more specific at the receptor but clonidine is still widely used in Europe. There are no studies with head-to-head comparison of these two drugs, their analgesic efficacy seems comparable but risk–benefit profiles may differ.¹⁶ The best dose, timing, and route of administration needed to produce maximum benefit and minimum harm are largely unknown.

Role in preventive analgesia

Currently there is no evidence to show that perioperative α_2 agonists have a preventive analgesic effect. None of the trials included in the systematic review showed that α_2 agonist had analgesic effect lasting >48 h. There was also no data on chronic postoperative pain or hyperalgesia.

Conclusion

Non-opioid adjuvant analgesia has a definite role in perioperative settings. These drugs act by modifying the peripheral and central changes in the nociceptive system that occurs as a result of tissue injury. Definitive high-quality evidence for their use is variable, making it difficult to identify the best agents to use in individual patients. Targeting their use at patients most at risk of severe acute postoperative pain, of acute neuropathic pain, or risk of developing CPSP seems to be the most logical way to use them. This should avoid patients being unnecessarily exposed to their potential adverse effects. Among all these drugs, only ketamine, gabapentinoids, i.v. lidocaine, and α_2 agonists have some supportive evidence. Considerably more work is required to define optimum dosages, duration of treatment, and route of administration.

Declaration of interest

None declared.

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Appendix NHMRC levels of evidence

Level I	Evidence obtained from a systematic review of all relevant randomized controlled trials
Level II	Evidence obtained from at least one properly designed randomized controlled trial
Level III-1	Evidence obtained from well-designed pseudo-randomized controlled trials (alternate allocation or some other method)
Level III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomized (cohort studies), case-control studies, or interrupted time series with a control group
Level III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
Level IV	Evidence obtained from case series, either post-test or pre-test and post-test

Please see multiple choice questions 5–8.