Review Article

Reducing opioid use perioperatively: a narrative review

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Objective: With the increasing incidence of opioid misuse worldwide, much more focus has been placed on the widespread use of these drugs in the perioperative period. This narrative review article discusses recent literature and some of the adjunct analgesic techniques that can be used to minimise opioid use perioperatively.

Background: In addition to addiction and dependence, there are multiple adverse effects associated with opioids that it can be beneficial to avoid, especially as enhanced recovery programmes have become more universal. In this review article, we discuss some common analgesic adjunct medications such as alpha-adrenoceptor agonists, ketamine, gabapentinoids and lidocaine, and the evidence behind their use perioperatively with regards to opioid sparing and patient outcomes.

Methods: A range of electronic databases were consulted to conduct a literature search including PubMed, MEDLINE, Embase and the Cochrane Library. Keywords included perioperative, opioid, opiate, adjunct, opioid-free, opiate-free. References of identified studies were then manually searched to find further relevant papers.

Conclusions: While the evidence we review here suggests that opioid free anaesthesia or analgesia may be feasible, there is a lack of sufficient robust evidence and concerns regarding safety of adjunct medication mean that best practice may lean towards opioid minimising where possible, as supported by international consensus.

Keywords: Opioid; adjunct; enhanced recovery; perioperative

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Introduction

Opioids are currently a cornerstone of perioperative pain management; in a 2016 review of nearly 800,000 patients undergoing surgery, 97% received opioid analgesia (1). As the incidence of postoperative opioid prescription has risen, so too has the incidence of misuse of these drugs, with prescription opioids now the leading cause of drug related overdoses in the United States (2). It is estimated that three-quarters of illicit heroin users in the United States started first with prescription opioids (3,4). Clearly not all of these prescriptions would be for postoperative patients, but it goes against the traditional teaching from the 1990s that patients can't become addicted to opioids if being treated for pain (5). Some studies suggest that up to 1 in 10 patients can become persistent users of opioids after surgery; if classed as a postoperative complication, this would make it one of the most common after elective surgery (6,7). In addition, reduction of perioperative opioids can lead to a decrease in adverse perioperative outcomes such as postoperative nausea and vomiting (PONV), postoperative ileus, hyperalgesia, sedation and urinary retention (8).

The origins of the opioid crisis came from honorable intentions, with a push to treat pain as the 'fifth vital sign' (9).

Table 1 Non-opioid adjuncts and their mechanism of action

Adjunct medication	Mechanism of action in analgesia
Alpha-adrenoceptor agonist (e.g., clonidine, dexmedetomidine)	Alpha-2 adreno receptor agonism in the substantia gelatinosa of the dorsal horn in the spinal cord. Dose-dependent inhibition of release of nociceptive neurotransmitters, e.g., substance P
Ketamine	N-methyl d-aspartate (NMDA) receptor antagonist with action at μ and k opiate receptors
Gabapentinoids (e.g., pregabalin, gabapentin)	Selective inhibition of the alpha-1 delta-1 subunit on voltage gated calcium channels. Decreased release of noradrenaline, substance P and glutamate
Lidocaine	Unknown. Blockade of sodium channels in neural tissue

This also coincided with more aggressive pharmaceutical advertising of opioid based analgesia strategies (10).

Another potential worry with regard to high rates of opioid use in the perioperative period is the effect on opioids on cancer metastasis recurrence. It is postulated that opioids may have a dose-dependent effect on natural killer cell cytotoxicity and proinflammatory cytokine production (11). Some studies have demonstrated better cancer outcomes with regional anaesthesia, and one of the possible mechanisms behind this effect could be the avoidance of opioids (12). The data is not clear cut and there is mixed animal evidence both for and against this theory; a recent meta-analysis of animal data concluded that opioids have no overall effect on tumour progression (13). While it may be of genuine clinical concern, current evidence in human medicine appears to suggest that if opioids have any effect on tumour progression there is negligible clinical impact (14).

In view of the above, much interest has arisen around opioid free or opioid minimising techniques for providing analgesia in the perioperative period, especially with the popularity of enhanced recovery programmes. This review article aims to give an overview of some of these techniques and the evidence behind them.

The majority of current evidence with regards to opioid minimising anaesthetic techniques is limited to case studies and reports and there is a lack of large randomised control trials. Most cases used a combination of paracetamol and non-steroidal anti-inflammatories with intravenous infusions of alpha adrenoreceptor agonists or ketamine (15,16). Dexmedetomidine and lidocaine have been used as continuous infusions in pilot studies in combination with propofol or nitrous oxide without any opioid use (17,18). Regional anaesthesia use seems key to reduction of opioid use in most of these studies when surgically appropriate (19,20), but in this review article we have focused on the evidence for non-opioid adjuncts as presented in *Table 1*.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/dmr-21-92).

Non-opioid adjunct medications

In addition to commonly used medications such as paracetamol and non-steroidal anti-inflammatories, there are several adjunct medications that are freely available for perioperative analgesia. This article will review these adjunct medications and the evidence for their use in opioid sparing analgesic regimens.

Alpha adreno-receptor agonists

Dexmedetomidine and clonidine are both alpha adreno receptor agonists that have anxiolytic, sedative and analgesic effects, with dexmedetomidine being up to 8 times more selective for the alpha-2 receptor than clonidine. It is postulated that the analgesic effects of these drugs are through agonism of the alpha-2 adreno receptor in the substantia gelatinosa of the dorsal horn in the spinal cord, resulting in dose dependent inhibition of release of nociceptive neurotransmitters like substance P (21).

A 2016 Cochrane review of the use of dexmedetomidine in acute pain after abdominal surgery showed a reduction in opioid consumption in the postoperative period (22). However, the studies included were small and not homogenous, so the quality of evidence was felt to be poor, with limited data on potential adverse effects. A recent randomised controlled trial comparing remifentanil and fentanyl with an opioid-free regime using dexmedetomidine was stopped prematurely due to severe bradycardia in several patients in the intervention group (23). However, despite limited results, postoperative opioid consumption

and nausea were both decreased in the dexmedetomidine group. Clonidine is less selective for alpha-2 adrenoceptors than dexmedetomidine and although it has been shown to have opioid sparing properties it is less effective than dexmedetomidine (23). It is worth noting that dexmedetomidine is not yet licensed for use in theatres within the United Kingdom (24).

Ketamine

Ketamine is an N-methyl d-aspartate (NMDA) receptor antagonist with some action at opioid receptors. It is commonly used as an analgesic adjunct and has been shown to have opioid sparing effects perioperatively of up to 40% (25). A Cochrane review in 2018 showed that perioperative ketamine could reduce postoperative morphine use by up to 8 mg in the first 24 hours post-surgery (26). However, the postoperative use of ketamine may be limited as most studies use low dose intravenous infusions, which may not be practical outside of high dependency settings.

Adverse effects may limit the use of ketamine regularly for postoperative analgesia. Dissociative symptoms, hallucinations and increased confusion have all been reported, with an incidence of up to 9% following a single bolus dose (27). In addition, ketamine is not without it's own issues with regards to abuse and addiction with a prevalence of 0.8% in college students (28).

Gabapentinoids

Pregabalin and gabapentin (collectively known as gabapentinoids) are anti-epileptic drugs that have also got good evidence in usage for neuropathic pain (29). They exert their effects via selective inhibition of the alpha-1 delta-1 subunit on voltage gated calcium channels (30), decreasing the release of noradrenaline, substance P and glutamate. Data is limited on use of gabapentinoids for acute pain despite increasing use in surgical pathways, and they are not yet approved by the FDA in the United States for acute pain (31).

A 2015 systematic review and meta-analysis looking at perioperative gabapentin found a reduction in pain in the first 24 hours postoperatively with an associated reduction in PONV but an increase in sedation (32). Again, this meta-analysis was limited by study heterogeneity, with studies looking at a range of surgeries and doses of gabapentin ranging from 600 to 1,500 mg. A 2015 meta-analysis of the effect of perioperative pregabalin use showed similar results; a reduction in postoperative pain scores and opioid requirement but variation in doses used for optimal effect (33). These findings are challenged in a recent meta-analysis of 218 trials published by Verret *et al.* in 2020, where gabapentinoids were found to have no statistically significant analgesic effect on postoperative surgical pain but did show a greater risk of adverse effects (34). Most common adverse effects reported were dizziness and visual disturbances, and the opioid sparing effect was small and not clinically significant.

Lidocaine

Lidocaine is an amide local anaesthetic that exerts it's action through the interruption of neurological transmission by blocking sodium channels in neural tissue, although the mechanism by which it provides systemic analgesia is largely unknown (35). It was initially used as an anti-arrhythmic agent in addition to local or regional anaesthesia. It has become popular intravenously as an analgesic adjunct in recent years with proposed benefits including being opioid sparing, decreased postoperative pain, prevention of hyperalgesia and decreased postoperative ileus (36). Lidocaine is usually used as a bolus followed by an infusion for postoperative pain, although doses vary in different trials which can make evaluation of the evidence more difficult.

A Cochrane review in 2016 of 68 trails compared intravenous infusion of lidocaine to thoracic epidural, placebo or no treatment, and found low evidence that pain scores were improved at 24 or 48 hours, with little difference between surgical sub types (37). Doses used in the studies ranged from 1 to 5 mg/kg/hour, and the length of time infusions were used for similarly varied from the end of surgery to several days. With regards to prevention of adverse events, this review showed low quality evidence that intravenous lidocaine infusion had a statistically significant effect on adverse events such as postoperative ileus, postoperative nausea and opioid consumption.

Concerns regarding the safety of lidocaine remain due to its narrow therapeutic index. This has led to the recent publication of an international consensus statement (38) in 2021. Among the published recommendations were a dose of 1.5 mg/kg loading bolus followed by 1.5 mg/kg/hour infusion for not more than 24 hours within a high dependency unit, explicit informed consent should be obtained from the patient prior to use, and lidocaine should not be used in conjunction with any other local anaesthetic

interventions. These recommendations may be key in potentially limiting the use of lidocaine in opioid sparing analgesic regimes, particularly in surgical enhanced recovery programmes. The benefits of lidocaine must be balanced against the risks, and it's use in opioid free or sparing analgesia currently seems confined to a specific subset of patients.

Opioid free or opioid minimisation?

A recent meta-analysis of opioid free anaesthesia by Frauenknecht and colleagues analysed data from over 1,300 patients from 23 randomized controlled trials (39). They demonstrated that there was no difference in pain scores at 2 hours postoperatively, but perhaps unsurprisingly there was a significantly higher rate of nausea and vomiting in the opioid group. This however did not lead to an increased time in the postoperative recovery area.

Remifentanil was used as part of the anaesthesia protocol in fourteen of the studies. Remifentanil is an ultra-short acting intravenous opioid which is usually given as an infusion. At high doses it has been implicated in causing opioid induced hyperalgesia postoperatively (40), and so there is the question of whether the use of remifentanil falsely affected the pain scores in the recovery area. In this case, the findings could be due to the avoidance of remifentanil in the treatment group. This would be difficult to prove but shows the complexity of the factors in play here. Routine use of prophylactic antiemetics was not mentioned in either group; could this small difference in PONV have been overcome by prophylaxis, as now recommended in all enhanced recovery after surgery pathways?

The included studies were all limited to the intraoperative period. One of the perceived reasons for undertaking opioid free anaesthesia is to eliminate chronic opioid use, but none of these studies looked at this. In this case, can we even draw the conclusion that opioid free anaesthesia will reduce longer term opioid dependence? Further research could focus on the effects on chronic opioid use and longer term implications of low dose or opioid-free analgesic regimes. Finally, it should also be noted that many of these patients received intravenous rescue opioids. Fifteen of these studies (four did not specify) had parenteral opioids as a rescue therapy. So, a broader question should be asked, is this opioid-free anaesthesia at all?

This leads into a wider discussion about what "opioid free anaesthesia" actually entails. In their editorial, Elkassabany and Mariano attempted to define it as "*A perioperative care strategy that maximises non-opioid modalities for anaesthesia and analgesia and reserves the use of opioids for severe acute pain unrelieved by other methods from admission to discharge from the hospital*" (41). This seems a sensible and pragmatic definition. It allows a comprehensive multi-modal analgesic regimen (including the use of regional anaesthesia), but also permits cautious opioid use in the presence of severe unrelieved breakthrough pain.

While the evidence we have reviewed suggests that opioid free anaesthesia or analgesia may be feasible, the lack of sufficient robust evidence and concerns regarding safety of adjunct medication may mean that best practice tends towards one of minimizing opioid use (together with a multimodal analgesic regimen) rather than total opioid abstinence. Merely swapping the side effects of one (opioid) drug for another such as ketamine (with its dissociative symptoms and hallucinations) is not always the most beneficial approach for the patient. It is rare to have a patient who absolutely cannot have opioids, but opioid sparing techniques can be beneficial for many with the bonus of reduced rates of opioid dependence postoperatively. This seems to be the consensus of the international community, and in 2019, The American Society for Enhanced Recovery and Perioperative Quality released a statement that expressed a lack of sufficient evidence to recommend opioid free anaesthesia and analgesia over perioperative opioid minimisation (8).

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