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Non-opioid analgesic options

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Introduction

The provision of safe and effective perioperative analgesia forms one of the cornerstones of anaesthetic practice. Traditionally this has been achieved with a mix of paracetamol, non-steroidal anti-inflammatory drugs and opioids. Opioids have formed the backbone of our analgesic strategy for a number of years and can provide excellent analgesia. However the side-effect profile of these drugs can prove unsatisfactory. It is also important to be cognizant of the potential for abuse and addiction associated with even the short-term use of opioid analgesics. A cohort study in the British Medical Journal demonstrated that almost 50% of patients were discharged home with opioid prescriptions after elective surgery and that 3% of them were still taking opioids 90 days after surgery.[1] Rates of opioid use and addiction are not known in South Africa but with thousands of patients undergoing surgery annually it cannot be assumed that we are immune to the problems of opioid abuse. As such the use of non-opioid and non-traditional analgesics is gaining traction.

This talk will focus on the evidence for the use of non-opioid analgesics in the perioperative period.

Drugs to be discussed:

- Lignocaine
- Gabapentinoids
- Alpha 2 agonists

Lignocaine

Pharmacology:

Lignocaine is an amide local anaesthetic with a variety of uses. The mechanism of action has traditionally been described as blocking nerve conduction via blockade of the Na^+ channel on the membrane of neurons. Newer theories are that lignocaine blocks K^+ and Ca^{++} channels and interacts with G_q protein coupled receptors.[2]

Lignocaine is extensively metabolised in the liver and clearance from the plasma is related to hepatic blood flow. This explains why infusions of lignocaine can be used in patients with normal hepatic function with no significant accumulation and risk of toxicity.[2]

None of the above, however, fully explains the ability of intravenous lignocaine to produce significant analgesic and anti-inflammatory effects. Multiple theories have been put forward in order to explain the ability of lignocaine to produce clinically significant reductions in pain scores long after the drug infusion has been stopped.

These theories include[3]:

- Inhibition of polymorphonuclear granulocytes;
- Interaction with inflammatory coupled G_q protein receptors;
- Direct neuronal effects in the spinal cord.

What is clear is that there is a large body of evidence for the safe and effective use of IV lignocaine in the perioperative period in order to reduce pain scores, opioid consumption, nausea, ileus and length of hospital stay.

Abdominal surgery:

The evidence for the benefits of lignocaine infusion is perhaps greatest for intra-abdominal surgery, both open and laparoscopic.

In doses ranging from 1.5–3 mg/kg/hr after a bolus of 0–1.5mg/kg, intravenous lignocaine improves pain scores consistently. The Visual Analogue Scale (VAS) of patients is decreased immediately postoperatively and at 24 hours after surgery. Opioid consumption is decreased by an average of one third in patients receiving intraoperative lignocaine and total analgesic consumption is decreased by 35%. These benefits are demonstrated consistently across a wide range of both open and laparoscopic procedures. Patient comfort and satisfaction is also improved, with better mobilisation in the postoperative period. Lignocaine also shortens the duration of postoperative ileus by 8 hours and decreases the incidence of postoperative nausea and vomiting (PONV). Lignocaine also shortened hospital stay by 8–24 hours. The incidence of toxicity in the literature was very low.[3-8]

In patients undergoing colorectal surgery, lignocaine infusion was found to be as effective as epidural analgesia in terms of VAS score and opioid consumption. It may be considered as a viable alternative in patients in whom neuraxial analgesic techniques are contraindicated.[3]

The use of perioperative lignocaine is also beneficial in patients undergoing bariatric surgery and is associated with a significant reduction in morphine or equivalent opioid consumption. This is

especially important in these patients as they are at an increased risk of opioid related adverse events, particularly respiratory depression.[9]

With the above evidence, which includes a number of meta-analyses and a Cochrane review, it would appear that the use of intravenous lignocaine infusion for open and laparoscopic abdominal surgery presents a number of benefits and has a low risk of toxicity.

Evidence for the use of lignocaine in other types of surgery is less striking but there are some benefits. A summary of the evidence follows:

- Genitourinary surgery
  - Lignocaine infusion decreased postoperative VAS score by 60% and reduced opioid consumption by 50% in patients undergoing radical prostatectomy.[10]
- Breast surgery
  - While lignocaine had no effect in immediate VAS score or PONV incidence there was a significant reduction in chronic postsurgical pain in patients undergoing mastectomy. Chronic postsurgical pain can be a debilitating complication after mastectomy and thus the ability to prevent it is an important benefit of lignocaine.[11]
- Spine surgery
  - Reduced postoperative pain scores in the postoperative period. Improved quality of life at 1 and 3 months post surgery as well as a decreased incidence of postsurgical pain.[12]

The use of lignocaine in cardiothoracic, gynaecological and day-case surgery has not been shown to improve pain scores or outcome.[3]

In summary, the use of perioperative lignocaine infusion is safe and effective; particularly in abdominal surgery. A loading dose of lignocaine should be given at induction with an infusion commenced immediately and ideally continued postoperatively. The length of infusion postoperatively to gain maximum benefit appears to be 8 hours, but benefit is shown from infusions even as short as 1 hour postoperative.[3]

A suggested approach to the use of lignocaine for perioperative analgesia:

- Loading dose of 1.5 mg/kg at induction;
- Infusion of 1.5–3 mg/kg/hr throughout surgery
- Continue infusion of 1.5–2 mg/kg/hr postoperatively for at least 1 hour and ideally for 8–24 hours.
- Monitor for signs of toxicity (tinnitus, perioral numbness, arrhythmia).

Gabapentanoids

Pharmacology:

These drugs include gabapentin and pregabalin. They have been used extensively in the treatment of chronic neuropathic pain and chronic pain syndromes. Their mechanism of action is via inhibition of the alpha-2-delta calcium channel in pre-synaptic neurons. This results in reduced release of excitatory neurotransmitters such as glutamate, substance P and calcitonin gene-related peptide. Both drugs are rapidly absorbed orally, have high bioavailability, are not metabolised and are excreted unchanged in the urine. Pregabalin appears to have greater potential as a perioperative analgesic agent due to its more predictable pharmacokinetic profile. Common side effects include dizziness and somnolence.[2,13]

A systematic review by Tippana et al.[14] in 2007 showed that the use of gabapentin improved analgesia at rest and with movement and reduced opioid-related side effects in general surgical patients. Another meta-analysis from Engelman et al.[15] in 2010 reported that the perioperative use of pregabalin does decrease pain intensity and opioid consumption, but has no effect on PONV across various types of surgery.

More recently, the use of pregabalin in particular in the perioperative period has been investigated in a number of surgical procedures.

Park et al.[16] investigated the use of preoperative pregabalin as an adjunct to spinal anaesthesia for patients undergoing urogenital surgery, specifically transurethral bladder and prostate surgery. A single dose of pregabalin 150 mg orally two hours before surgery was compared with placebo. The pregabalin group had significantly longer sensory blockade and significantly reduced VAS scores at 6 and 24 hours postoperatively. There was no difference in adverse effects between groups. The authors postulate that pregabalin may reduce potassium evoked excitatory neurotransmitter release and that decreased preoperative anxiety may modulate the pain response.

For laparoscopic cholecystectomy, it has also been shown that gabapentin and pregabalin may modulate the pain response. Eidy et al.[17] randomised patients into three groups. Patients received 800 mg gabapentin, 150 mg pregabalin or placebo orally two hours before surgery. Pain intensity was significantly lower in the gabapentin and pregabalin groups, opioid consumption was higher in the placebo group and there was a lower incidence of PONV in the gabapentanoid groups. Furthermore, pregabalin proved to be superior to gabapentin for reducing postoperative pain scores.

Matsutani et al.[18] employed a slightly different pregabalin dosing regimen in their study that compared pregabalin with thoracic epidural analgesia in patients post thoracotomy. The pregabalin group received 75 mg orally twice daily from the day of surgery. Compared to patients who received thoracic epidural analgesia the pregabalin group had significantly lower pain scores and reported less sleep interference. This group also had less analgesic consumption after the first 24 hours postoperatively. There was no evidence of any increased adverse effects in the pregabalin group. The authors' conclusion is that pregabalin is a safe and effective alternative to thoracic epidural for post-thoracotomy pain.

From the available evidence, the use of pregabalin 150 mg orally before surgery should be considered. The use of pregabalin as an adjuvant to traditional analgesia postoperatively can also be considered. Caution should be employed in elderly patients and those with renal dysfunction.

Alpha 2 agonists

Clonidine and dexmedetomidine are drugs which act as agonists at the alpha 2 adrenergic receptor. The alpha 2 receptor is a G_i protein coupled receptor located throughout the central and peripheral nervous system. Activation of these G_i proteins causes inhibition of noradrenaline release and reduction in cell signaling. These drugs are sympatholytic and sedating without causing respiratory depression. Dexmedetomidine has a much higher affinity for the alpha 2 receptor with little alpha 1 effect compared to clonidine, which can act as an alpha 1 agonist at higher doses.[2]

Both of these drugs have shown analgesic properties in addition to their sedative effects. The mechanisms for these analgesic effects are not yet fully understood but are thought to be due to central and peripheral effects. Central effects are decreased sympathetic nervous system activation in the central nervous system with subsequent reduction in excitatory neurotransmitter release. There is also inhibition of nociception in the dorsal horn of the spinal cord.[2,19]

Peripherally these drugs appear to cause direct inhibition of nerve fibres, especially type C fibres and they may also have cross reactivity with opioid receptors and produce analgesia via interaction with G_q protein coupled receptors.[19]

Clonidine and dexmedetomidine can be administered via multiple routes: intranasally, intramuscularly, intrathecally and combined with local anaesthetics for peripheral nerve block. Additionally, clonidine can be administered orally.

The following is a summary of the latest available evidence for the perioperative use of alpha 2 agonists.

Clonidine:

Clonidine has advantages in that it can be given as a single dose in the perioperative period.

Samantaray et al.[20] gave patients 3 µg/kg of intravenous clonidine versus placebo in patients undergoing thoracic surgery. Postoperative VAS score and opioid consumption was significantly lower in the clonidine group. The group receiving clonidine was slightly more sedated than the placebo group immediately after extubation but there was no difference in sedation score upon discharge from the recovery room.

During open cholecystectomy, clonidine 3 µg/kg intravenously again showed to provide superior analgesia, better pain scores and lower opioid consumption. A second group in this study received clonidine infiltration into the wound and also had lower pain scores and analgesic requirements. This clearly shows that there are peripheral antinociceptive mechanisms behind the action of the alpha 2 agonists.[21]

A single intravenous dose of clonidine of 1-3 µg/kg is safe and effective in reducing postoperative pain. It can also be considered in patients in whom opioids may be high risk and it is also an effective analgesic in children.

There are also other non-analgesic benefits to the use of clonidine such as sedation, anxiolysis, reduced PONV, reduced shivering, and mitigation of the surgical stress response. It is also effective as a supplement to neuraxial epidural anaesthesia at a dose of 1 to 1.5 µg/kg.[13,22]

Side effects to be cautious of are hypotension and bradycardia. Clonidine should always be given slowly.

Suggested doses of clonidine:

- Epidural and caudal: 1–1.5 µg/kg
- Wound infiltration: 2–3 µg/kg
- Intravenous: 1–3 µg/kg

Dexmedetomidine:

Dexmedetomidine is an alpha 2 agonist with an eight times higher affinity for the receptor than clonidine. It was initially only indicated for use in the ICU setting as a sedative agent for ventilated patients. It has subsequently been approved for use in the perioperative setting in non-ventilated patients. The intravenous use of dexmedetomidine was initially recommended to begin with a loading dose followed by a maintenance dose. The loading dose has largely been abandoned due to unfavourable side effects of bradycardia and reflex hypertension.[2]

A 2017 review in the Journal of Pain Research looked at the effects of dexmedetomidine used via various routes. Intranasal premedication with dexmedetomidine at a dose of 1–2 µg/kg for children undergoing various ear, nose and throat procedures was found to reduce postoperative pain and analgesic requirements.[23]

The use of dexmedetomidine in epidural anaesthesia at a dose of 1 µg/kg combined with local anaesthetic was associated with superior onset of analgesia, superior intraoperative analgesia, improved postoperative analgesia, better patient comfort and had minimal side effects. It was also shown to be superior to the epidural administration of clonidine. The addition of dexmedetomidine to caudal analgesia in children has also been shown to provide long lasting analgesia with stable haemodynamic parameters and no side effects. Intrathecal administration of dexmedetomidine was also associated with longer duration of spinal anaesthesia but was associated with significant episodes of bradycardia, some requiring treatment.[23]

There is limited evidence around the use of a single dose of intravenous dexmedetomidine. It is most commonly administered as an infusion throughout the operative period and indeed a single intravenous push of dexmedetomidine is associated with significant bradycardia. In patients undergoing total abdominal hysterectomy the intravenous use of dexmedetomidine during the intraoperative period was associated with lower VAS scores postoperatively and lower opioid consumption. These benefits continued up to three days

Table 1. Summary of suggested doses of non-opioid analgesics

Lignocaine	Gabapentinoids	Clonidine	Dexmedetomidine
Loading dose of 1.5 mg/kg at induction	Pregabalin 150 mg orally two hours before surgery	Epidural and caudal: 1 to 1.5 μg/kg	Intranasal premedication: 1–2 μg/kg
Infusion of 1.5–3 mg/kg/hr throughout surgery	Gabapentin 600 mg orally two hours before surgery	Wound infiltration: 2–3 μg/kg	Epidural and caudal: 1 μg/kg
Continue infusion of 1.5–2 mg/kg/hr postoperatively for at least 1 hour and ideally 8–24 hours.	Pregabalin 75 mg orally as an addition to postoperative analgesia	Intravenous: 1–3 μg/kg	Intravenous: infusion of 0.2–0.8 μg/kg/hr

post surgery, long after the dexmedetomidine infusion had been stopped. There was also less PONV.[24]

A 2016 Cochrane Review into the perioperative use of dexmedetomidine for abdominal surgery concluded that there is a decrease in analgesic requirements and VAS score with improved patient satisfaction. A firm conclusion on secondary outcomes (PONV, gastrointestinal function and mobilisation) could not be made.[25]

While generally more haemodynamically stable than clonidine it is important to always administer dexmedetomidine slowly and as an infusion when given intravenously.

Suggested doses for the perioperative use of dexmedetomidine:

- Intranasal premedication: 1–2 μg/kg
- Epidural and caudal: 1 μg/kg
- Intravenous: infusion of 0.2–0.8 μg/kg/hr

Conclusion

While opioids remain the backbone of our analgesic armament, it is vital that as anaesthetists we are cognizant of their adverse effects as well as the potential for abuse and addiction. As such, any strategy to reduce the use of opioids in the perioperative period should be embraced. The drugs discussed are certainly not new but their use as non-opioid and adjuvant analgesics is gaining popularity and there is ongoing research into their analgesic benefits. When used alone or in combination in appropriate patients and surgical procedures they are indeed safe and effective.

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