

Opioid Free Anaesthesia: a paradigm shift

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Introduction

Opioids have been the cornerstone of analgesia under anaesthesia since the 1960's and were introduced to provide haemodynamic stability in this setting.¹ The routine use of synthetic opioids, although rarely questioned, should be supported with evidence which favours patient outcomes in the perioperative period.² As physicians, best practice evidence guides our hand in rendering favourable outcomes to our patients. Therefore, it is prudent to question whether or not there are alternative methods to managing pain in the perioperative setting.

Why opioid free anaesthesia?

Opioids have served anaesthesiologists well in rendering haemodynamic stability and reduced nociception to their patients, but have also caused many complications because of their side effect profile and the candid nature with which they are used. This unconsidered use of opioids has led to the so called 'opioid crisis'.^{3,4}

What is the opioid crisis?

In the United States, doctors prescribe and patients consume a staggering 80% of the world's supply of opioids despite only making up approximately 4.4% of the world's population.⁵

In just over a decade, opioid prescriptions quadrupled and opioid related deaths surpassed motor vehicle accidents as the leading cause of accidental death.^{6,7}

Since the treatment of pain is constitutionally a basic human right, and costs nations millions in medical treatment and loss of productivity, there has been a pendulum swing unintentionally towards the increased use of opioids. However, this has led to the overwhelming overuse and abuse of opioids that is now deemed to be 'in crisis'.⁵

As Anaesthetists, we play an important role in the promulgation of this crisis through postsurgical pain management. Retrospective studies show that between 3% and 7% of opioid naïve surgical patients still use opioids their first year after surgery.^{8,9} The risk of chronic opioid abuse is significantly increased in surgical patients when compared to non-surgical patients¹⁰ and it is therefore the responsibility of the perioperative physician to add good governance to prescription practices so as to curbe the added risk of potential addiction to postoperative patients. To reduce the burden of hospital discharge, doctors are incentivised to

overprescribe post hospital opioids. This results in up to 72% of the pills prescribed going unused by general surgical patients.¹¹ It has been shown that this strategy leads to opioids falling into the wrong hands and exacerbates drug addiction problems.^{12,13}

Therefore, opioids are under the spotlight as a leading cause of morbidity and have consequences that are not only patient specific, but affect society and the economy.

The reason behind opioids being so addictive and propagating this knock-on effect is because of the pathophysiological process known as neuroadaptation.

Neuroadaptation

The major features of opioid addiction are tolerance, withdrawal and compulsive use and relapse. These are thought to be brought about by a large range of neuroadaptations in response to chronic opioid exposure.¹⁴

Adaptations to opioid exposure are considered to occur at different levels in the nervous system and include:

- tolerance at the mu-opioid receptor
- cellular tolerance and withdrawal in opioid-sensitive neurons
- systems tolerance and withdrawal in opioid-sensitive nerve networks
- synaptic plasticity in opioid-sensitive nerve networks

Tolerance to opioids is characterised by a reduced clinical response to opioid agonists, manifesting as increasing dose requirements to achieve the desired effect. Mechanisms of receptor regulation appear to be enhanced as a result of *receptor* tolerance and include desensitisation and internalisation.¹⁴

Cellular tolerance is more complex and several processes are involved which include the upregulation of cAMP/PKA and cAMP response signalling as well as the mitogen PK cascade.¹⁴

The complex neuropharmacology of neuroadaptation is out of the scope of this discussion, but is important to the understanding of why opioid free anaesthesia (OFA) may offer better anaesthetic care in the face of the opioid crisis. Furthermore, neuroadaptation is just one of many consequences to opioid use peri-operatively and thereby supports efforts to seek alternative perioperative analgesic practices.

The threat of opioids

The consequences of opioid administration intra- and postoperatively are not benign or uncommon and include:

- Nausea and vomiting
- Sedation
- Ileus
- Confusion/delirium
- Respiratory depression
- Increased postoperative pain and morphine consumption¹⁵
- Immunodepression
- Potential hyperalgesia
- Chronic postoperative pain
- Addiction

Hypoxaemia, ileus and confusion/delirium are among the most commonly seen complications, which are associated with significant morbidity.¹

Hypoxaemia

This is a frequent complication post-anaesthesia and occurs within minutes after extubation. Patients undergoing abdominal surgeries have a high incidence of postoperative hypoxaemia, between 20%–40%^{16,17} which is attributed largely to the use of drugs such as opioids.¹⁸ In the USA, it is well described that a large majority of closed claims are the result of severe postoperative respiratory depression occurring within the first 24 hours post-surgery.¹⁹

Ileus

Postoperative ileus and its sequelae are one of the most important causes of prolonged hospitalisation from abdominal surgery. This is further complicated by the use of opioids that are often needed to manage pain.¹ More serious complications of ileus include:

- Gastrointestinal perforation
- Nosocomial infections
- Malnourishment
- Muscular atrophy

Complications exacerbated by the concomitant use of opioids in patients with ileus include:

- Bowel dysfunction
- Postoperative ileus in non-abdominal procedures
- Prolonged recovery

The incidence of ileus can be as high as 10%, as shown in recent reviews and was higher when higher doses of morphine was used.^{1,20}

Delirium and postoperative cognitive dysfunction (POCD)

Delirium and POCD are common in geriatric patients (5%–15% and 25%–40%, respectively), especially those coming for arthroplasty procedures. Delirium is associated with further cognitive decline that may lead to accelerated onset of dementia.^{21,22} Furthermore, they are associated with a longer

length of stay and discharge to monitored care environments. Overall, the incidence of 1 year mortality is higher in this patient population. Postoperative opioid analgesic practice in this group of at-risk patients is of particular concern, as the administration of intravenous opioids has been shown to significantly increase the risk of elderly arthroplasty patients developing POCD.²⁰ Krenk et al.²³ showed that fast track set ups that disallow for prolonged hospital stays and utilise opioid-sparing or opioid-free practice, avoids the development of delirium post operatively and hence reduces the risk of POCD and mortality.²³

Acute tolerance/hyperalgesia

The more opioids given intraoperatively, the more the postoperative analgesic requirements: this is termed the 'opioid paradox' and can be explained through acute tolerance and neuroadaptive processes caused by short acting opioids or chronic opioid use. It has therefore been suggested by several authors that the fewer opioids given intraoperatively the less opioid will be required postoperatively, because mu-receptor integrity is maintained.²⁴

Therefore, the revolutionary status that opioids have held because of their usefulness in creating a balanced anaesthetic now appears to be under duress. The rising evidence in favour of opioid restricted or non-opioid anaesthesia, although scarce, appears promising. Furthermore, in the context of enhanced recovery programmes, there is congruency and synergism with OFA that negates the negative effects opioids have had in abdominal procedures. OFA has therefore been pushed into the spotlight as a potential solution to perioperative analgesic management that extends beyond its use in only abdominal surgeries.

Opioid Free Anaesthesia

The basis of successful fast-track surgery is the use of efficacious multimodal analgesia and anaesthesia, and has been recommended for over a decade now to negate the potential deleterious effects of opioid overuse/abuse. These multimodal, opioid avoiding drug regimens aim to decrease intraoperative and postoperative opioid requirements, decrease postoperative pain, and hence hasten recovery through avoidance of potential side effects caused by opioids.²⁵

Opioid-free anaesthesia (OFA) is a multimodal anaesthetic practice that utilises:

- Hypnotics
- Gabapentinoids
- N-methyl-D-aspartate (NMDA) antagonists
- local anaesthetics
- anti-inflammatory drugs
- alpha-2 agonists

The abovementioned OFA drugs were discussed in last year's North West Refresher notes and hence will not be repeated here.²⁶ Instead, the focus of this discussion is to inform about specific OFA protocols and debate whether we should be practicing them.

Concerns over providing haemodynamic stability with OFA are abated by evidence provided in the first studies concerning OFA, which focused on bariatric patients. The use of dexmedetomidine, was shown to significantly reduce postoperative pain and opioid requirements in this patient population, without causing respiratory depression.^{27,28} Furthermore, the use of dexmedetomidine permits haemodynamic stability under anaesthesia, due to its unique spinal and supraspinal mode of action. Several studies^{27,28} have gone on to show the positive effects of OFA with dexmedetomidine, which include:

- sparing of other anaesthetic agents
- improved haemodynamic stability
- reduced bleeding
- prevention of shivering
- non-delayed emergence
- attenuated postoperative pain
- reduced postoperative opioid consumption
- reduction in postoperative nausea and vomiting
- prevention and treatment of hyperalgesia

The significance of hypotension and bradycardia caused by dexmedetomidine is yet to be determined, as there is no evidence currently on the consequences of the use of alpha-2 agonists intraoperatively.²

Loco-regional anaesthesia also forms part of OFA principles, as they negate the need for intraoperative and postoperative opioids. Peripheral nerve blocks and epidurals improve pain management significantly. Furthermore, epidurals have been shown to prevent, independently from the use of opioids, postoperative hyperalgesia.²⁹ Local anaesthetic adjuncts now also include alpha-2 agonists in their armamentarium, and thus provide safer block prolongation without the unwanted side effects of opioids.²

Ketamine has an important role in OFA, as its use improves the management of postoperative pain, through its analgesic, anti-hyperalgesic properties and haemodynamic safety profile.²

To further abate concerns over providing a haemodynamically stable anaesthetic with OFA, adding magnesium sulphate to OFA protocols, is shown to not only augment the analgesic action of lignocaine and ketamine, but importantly reduces heart rate variability without causing hypotension.²

The abovementioned drugs form part of most OFA regimens and are not complete without the mention of intravenous lignocaine. Lignocaine use intravenously is advocated in major surgeries, especially abdominal surgeries, because of its complimentary effects to enhanced recovery programs i.e. anti-inflammatory properties, pro-peristaltic action, sympathetic blockade and acute analgesic action.

Although scarce, the available evidence advocating opioid sparing techniques is in favour of their use. However, it is not clear whether there is overall benefit to completely abdicating the use of opioids. The Postoperative and Opioid Free Anaesthesia (POFA) randomised-controlled trial is underway (NCT03316339)¹, and hopes to test the superiority of OFA techniques, but to also test non-inferiority and safety of OFA.¹

Perhaps the most famous protocol to date is the Bruge Protocol developed at Sint Jan Brugge to treat patients coming for major bariatric surgeries.

OFA Protocol Sint Jan Brugge with Dex

Three drugs (Dex 200ug, Ket 50 mg, Lid 300 mg, add H2O to 20 ml) given at 1 ml/10 kg IBW and followed by 1 ml/10 kg IBW/h adapt to HR/MAP

- Dexmedetomidine 0,5 to 1 ug/kg IBW followed by 0,5 to 1 ug/kg IBW/h
- Ketamine 0,125 to 0,25 mg/kg followed by 0,125 to 0,25 mg/kg IBW/h
- Lidocaine 1,5 mg/kg IBW followed by 1,5 to 3 mg/kg IBW/h

Magnesium sulphate 40 mg/kg IBW followed by 10 mg/kg IBW/h

Propofol is given at 2,5 mg/kg IBW followed by inhalation anesthesia at 0,6 - 0,8 MAC with BIS around 40%.

Rocuronium 0,6 - 1 mg/kg IBW followed by infusion 1 mg/kg IBW/h and based on TOF PTC (if NMB is needed).

Postoperative analgesia

Non-steroidal anti-inflammatory agents

- Paracetamol 2 g loading 1 g/6h
- Diclofenac 150 mg loading, 2x75 mg/day
- Or Keterolac 40 mg loading, 3 x 10 mg/day

Local wound infiltration (calculate toxic dose!)

Choice between:

- Continue with clonidine 2 x 75 ug/day or give low dose morphine

OR

- Keep infusion of sympatholytic mixture (ket dex lido Mg) at low dose without deep sedation
 - Ketamine 0,05 mg/kg/h
 - Lidocaine 1 mg/kg/h
 - MgSO₄ 10 mg/kg/h
 - Dexmedetomidine 0,1 - 0,2 ug/kg/h

Monitoring and ensuring safe OFA

One of the valid concerns, regarding OFA, is the lack of adequate tools to monitor nociception (sympathetic/parasympathetic balance). This, however, brings into question how accurate any nociceptive monitoring is, especially since it is not routine and anaesthetists rely mainly on the haemodynamic status to address 'pain' under anaesthesia.²⁴

Noxious stimuli from surgical stress induces neuro-humoral activation and therefore cardiovascular and pulmonary effects that can be objectively monitored and documented through standard ASA monitoring under anaesthesia. This is effective in monitoring opioid-based anaesthetic practice, but is not specific to surgical stimulus and nociceptive activation exclusively.²⁴

The 'pain matrix' or brain network responsible for the sensory processing of nociception and pain is associated not only with cortical activity but sub-cortical activity too, thus making it a highly complex network. Therefore, monitors such as BIS or Entropy, which monitor processed cortical EEG brain activity,

do not assess the effects of nociception. This is corroborated by Lichtner et al. who demonstrated that propofol cannot alter noxious stimuli effects at the spinal level nor at midbrain level, even at burst suppression doses.²⁴

What tools do we have then, to monitor the stress response effects, when using OFA?

Autonomic system evaluation

The measurement of sympathetic activity and heart rate variability through skin conductance methods as well as surgical plethysmography index tools have shown some promise in detecting acute pain in anaesthetised patients, however their accuracy clinically has never been shown to be clinically significant.³⁰ More recently, a French company, Metrodoloris, has been promoting the use of the Analgesia Nociceptive Index (ANI), which is promoted as a potential tool to aid the assessment of acute nociception and pain.²⁴

ANI works on the basis of raw ECG data that is derived from the use of two ANI electrodes that are applied in the V1 and V5 positions on the chest. Frequency domain-based analysis of the high frequency component of HRV combined with respiratory rate computes the ANI, which is displayed as a number from 0-100. The values reflect predominance in parasympathetic tone, with low numbers being low tone and high numbers being high parasympathetic predominance.^{31,32}

Despite there being a large number of publications regarding ANI-guidance for intraoperative opioid administration, there is weak evidence supporting that it improves pain post-operatively. This makes it less likely to be useful as a tool for monitoring pain in the setting of OFA anaesthesia.²⁴

Conclusion

In conclusion, the scarcity of evidence supporting the use of OFA in place of opioid based anaesthetic practice means that the obvious feasibility of OFA is not sufficient to be recommended formally. Yet, specific adverse outcomes from OFA in the literature are absent. This calls into question the added value of opioid use at all, since the use of opioids have such potential for adverse events postoperatively. The lack of research in a wide range of surgical procedures means that opioids still form the basis of perioperative analgesia, however, they have fallen out of favour in enhanced recovery programmes, due to the obvious benefits of OFA. This see-saw is where we are currently at determining the place of OFA and the POFA trial hopes to shed more light on this controversial topic.

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