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Opioid-Free Anaesthesia

M Patel

Moderator: J Kibirige

UNIVERSITY OF
KWAZULU-NATAL

INYUVESI
YAKWAZULU-NATALI

School of Clinical Medicine

Discipline of Anaesthesiology and Critical Care

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INTRODUCTION

The provision of anaesthesia is often described in the context of the traditional triad of hypnosis, paralysis, and analgesia. [1] Achieving this with a single agent often requires high doses and may lead to haemodynamic instability – a concern recognised as early as 1926, when the concept of 'balanced anaesthesia' was first introduced. [2] This concept evolved over subsequent years, and in 1946 Gray and Halton propagated the practice of using separate agents for each goal to reduce the doses required. The analgesic component of the triad was typically achieved using opiates, such as morphine or pethidine, and with the development of newer agents, the opioid class has remained a cornerstone of anaesthetic practice ever since. [3]

Unfortunately, opioids are associated with a number of adverse effects. Combined with the shift in anaesthetic practice to not only alleviate pain, but also minimise other short- and long-term negative outcomes in the peri-operative period, this has led to the concept of opioid-free anaesthesia (OFA). Simply put, OFA describes an approach in which opioids are completely omitted during the intra-operative phase and replaced with a combination of non-opioid analgesics and adjuvants. Depending on the definition used this opioid-free period may include the pre-operative phase as well. [4, 5]

THE RATIONALE FOR OPIOID-FREE ANAESTHESIA

Avoidance of Opioids

The first goal of OFA is to address the adverse effects caused by opioids by preventing a patient's exposure to them. Post-operative side effects of concern include gastro-intestinal disturbances, CNS depression, and respiratory impairment. [3, 6]

In addition to reducing these side effects, OFA also helps to mitigate opioid-induced hyperalgesia. Although most often associated with Remifentanil, it has also been demonstrated with fentanyl and morphine. [3, 7] The mechanism behind opioid-induced hyperalgesia is not fully understood. Current literature supports the hypothesis of a dysfunction in the descending pathways, as well as an upregulation of central NMDA receptors playing an important role. [7] Interestingly, the same mechanisms may also be linked to opioid tolerance, despite hyperalgesia and drug tolerance being separate entities. [7] Both are of significance in the post-operative period, where pain control can dramatically affect a patient's experience and progress.

Lastly, opioid dependence is a growing concern, but is mainly associated with longer periods of opioid use. [3] Whilst often thought of as a first-world issue, a South African study conducted in 2022 reported 0.1% of private patients (in their sample of over 1.2 million) had some form of opioid-use disorder, while the national household survey in 2012 reported that an estimated 0.3% of people 15 years or older had used some formulation of heroin (such as 'whoonga') in the last three months. [8]

Added Benefits of OFA

The advantages of opioid-free anaesthesia, however, are not simply the evasion of the issues described above. OFA reduces post-operative nausea and vomiting (PONV), has an opioid-sparing effect on analgesic requirements after surgery, and improves patient satisfaction. [4] Furthermore, it couples well with the principles within the enhanced recovery after surgery (ERAS) guidelines, as they also support the multimodal analgesic approach that is so integral to OFA. [9] The biological foundation for this is discussed below.

PAIN PHYSIOLOGY – WHY MULTIMODAL ANALGESIA WORKS

Basics of Nociception

At the cellular level we have nociceptors – specific receptors that occur throughout the body and respond to noxious stimuli. They may be activated by a variety of means, including pressure, temperature, inflammatory damage, and chemical substances. Activation of a nociceptor results in the depolarisation of the first-order nociceptive nerve fibre (typically type A-delta or C). The signal is then conducted along the ascending tracts to the brain, where it is interpreted and responded to. [10]

Contextualising Nociception within the Pain Pathway

The pain pathway categorises the event of a painful experience into four sequential steps: transduction, transmission, modulation, and perception. Transduction is the initial process of converting the stimulus at the nociceptor to an electrical form that may be sent along the nervous system, whilst transmission is the movement of the electrical signal from the first to the third-order neurons in the brain. [11]

Modulation is where the process starts to go beyond the somewhat straightforward route that has been described so far. It is the alteration of pain signalling, and may either facilitate (increase) or inhibit (decrease) the final signal product. This alteration may occur peripherally and/or centrally. Peripheral modulation is usually in the form of nociceptor sensitisation – in which the latency and threshold required for stimulation drops, the frequency of signal propagation escalates, and local hyperalgesia may occur. Central modulation may also be in the form of sensitisation (discussed below) or suppression (via substances such as serotonin and endogenous opiates). [11]

Lastly, perception refers to the cognitive and behavioural reaction to final signal that was sent from the thalamus to the cerebral cortex. [11] It is this final step of perception which highlights the difference between pain and nociception. As defined by the International Association for the Study of Pain, nociception is the “neural process of encoding noxious stimuli”, whereas pain is “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”. [12] In the context of a general anaesthetic, this then directs our intra-operative focus to nociception, as pain would require awareness to experience.

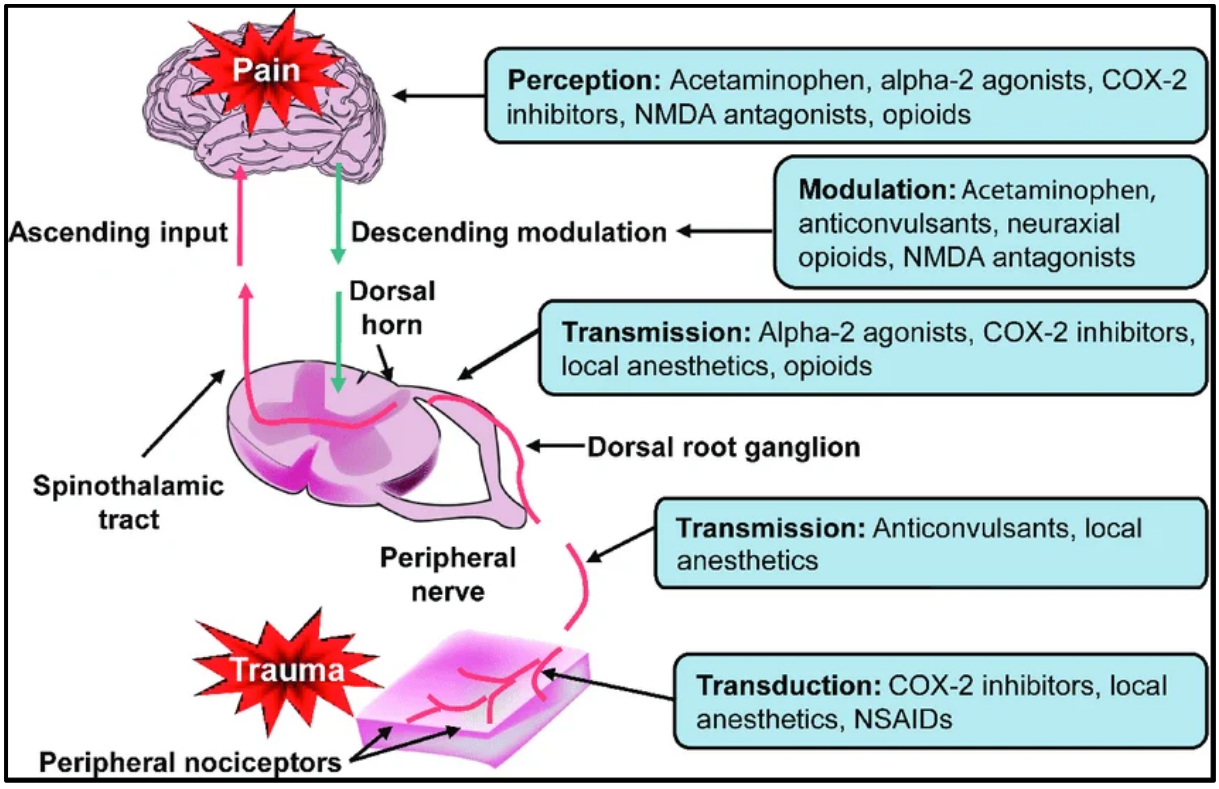
Central Sensitisation

Central sensitisation refers to an increase in the activity of central nervous system (CNS) neurons within nociceptive pathways, by means of augmented excitability and diminished inhibitory action. [13] The results of this include enhanced nociceptive action potentials and recruitment of adjacent non-nociceptive neurons to now respond to noxious stimulation (where they did not previously). [11, 13] While central sensitisation clearly has similarities to that seen in the peripheral nervous system, the neurons in the CNS are no longer coupled to nociceptors, and activation of the pathway at this level does not require a noxious stimulation. This leads to allodynia, and has been postulated as a mechanism for some forms of chronic pain. [13] At a biochemical level central sensitisation has been linked to excitatory effects of substance P, neurokinin A, and neurokinin B – all of which trigger a more powerful post-synaptic depolarisation, causing activation of the N-methyl-D-aspartate (NMDA) receptor and producing an uptick in excitatory amino acids via nitric oxide. [11, 13] Opioid-induced hyperalgesia is thought to be a form of central sensitisation

The Impact of Multimodal Analgesia

The pain pathway above exposes multiple locations and manners in which a signal may be intercepted or attenuated by analgesic agents. This is best appreciated via Diagram 1, which illustrates the steps in the pain pathway as well as which classes of analgesics may exert their effect at each point.

Diagram 1: Site of analgesic action along the pain pathway [14]



As we can see, no single class exerts its effect at all levels of the pathway. Moreover, whilst drugs may act at multiple sites, its strength and significance may vary. The mechanism of action is also of importance, as drugs typically function with specific receptors and transmitters – thereby limiting our anti-nociceptive ability or increasing the likelihood of adverse effects due to the dose required for adequate relief. Multi-modal analgesia techniques combat this by targeting multiple sites and mechanisms, providing the patient with superior anti-nociception and minimal side effects. [4] In the context of OFA, this idea extends further to assert that a multimodal approach is effective enough to not require opioids at all, but still obtain sufficient results. To do so, however, requires an intimate understanding of the options available and how to use them appropriately for opioid-free anaesthesia.

PHARMACOLOGICAL AGENTS USED IN OFA

The majority of drugs used for OFA fall within the classes listed in Diagram 1 (above). The main systemic intra-operative analgesics are Ketamine, α2-agonists, and Lignocaine, whilst the main adjuvant drugs used in OFA include magnesium, Esmolol, Dexamethasone, and gabapentinoids. [14] Factors for their use in the context of OFA are outlined below.

To note, regional anaesthetic techniques and simple analgesics (paracetamol, non-steroidal anti-inflammatory drugs) also form an important part of the multimodal approach, and should be considered when indicated and safe to use. [9]

Ketamine

Ketamine is primarily an NMDA receptor antagonist, but may also have activity on dopaminergic, serotoninergic, adrenergic, and cholinergic sites. It is a versatile drug which can be used for analgesia, sedation, or anaesthesia. It has also been investigated in the management and prevention of chronic pain due to its effects being at the NMDA receptor, where aspects of central sensitisation is thought to occur. In opioid-free anaesthesia it is typically administered as an intravenous infusion. [15]

- Dose
  - Loading dose 0.15-0.5 mg/kg (IV bolus); 0.15-0.3 mg/kg/h (infusion)
  - Dosing < 0.6 mg/kg considered non-dissociative
- Pros
  - Opioid-sparing effect
  - Not a respiratory depressant
  - Synergistic effect with magnesium
  - Anti-inflammatory effects (reduces IL-6, TNF-α, and NO levels)
  - Non-inferior analgesia versus opioids in emergency setting
- Cons
  - Psychomimetic symptoms may occur at doses above 0.3 mg/kg

- Dizziness, sedation, PONV (though lower frequency than with opioids) [15, 16]

Alpha-2 Agonists

Alongside Ketamine, α2 adrenergic agonists have emerged as important agents in OFA due to their analgesic, sympatholytic, and sedative properties. They work both centrally and peripherally – causing inhibition of sympathetic outflow, prevention of nociceptive transmission in the dorsal horn, and activation of α_2 receptors on pre-synaptic membranes to inhibit pain signalling. The use of both Dexmedetomidine and Clonidine has been described for OFA, although the former has been the preferred choice in most cases due to its relatively favourable pharmacokinetics. [17, 18]

- Dose
  - Dexmedetomidine: 0.5-1.0 μg/kg (loading); 0.2-0.5 μg/kg/h (infusion)
  - Clonidine: 3 μg/kg
- Pros
  - Opioid-sparing
  - Anxiolytic
  - Reduced anaesthetic requirements
  - Reduced PONV
  - No respiratory depression
- Cons
  - Haemodynamic: bradycardia, hypotension (may be significant)
  - Post-operative sedation [17-20]

Lignocaine

The third major intra-operative analgesic for OFA is intravenous Lignocaine. Like other local anaesthetics, it is a sodium channel blocker and prevents the transmission of neuronal signals. The mechanism for its systemic analgesic effect is unclear. It has also shown anti-inflammatory and opioid-sparing properties. As with Ketamine and the α2-agonists, Lignocaine is also given as an infusion when utilised for OFA. [21]

- Dose
  - 1-2 mg/kg (loading); 0.5-3 mg/kg/h (infusion)
  - Most common infusion doses between 1-2 mg/kg/h
- Pros
  - Reduced post-operative pain and opioid consumption
  - Reduced volatile anaesthetic requirements
  - Gastrointestinal: reduced PONV, ileus, and time to first bowel movement
  - Decreased recovery time and length of hospital stay
  - Short context-sensitive half-life (does not accumulate after long infusions)
  - Possible benefit against development of chronic pain and cancer recurrence
  - Anti-inflammatory and anti-hyperalgesia effects
- Cons
  - Risk of systemic toxicity
  - Dosing conundrum if peripheral nerve block is also being performed
  - May impact cardiac conductivity (caution with AV block, cardiac failure)

- May precipitate seizures [21-23]

Magnesium

In contrast to the agents above, Magnesium is not a considered a direct analgesic agent, but rather an adjunct. Its beneficial effects are thought to be due to its antagonistic effects at the NMDA receptor and its modulation on calcium influxes, which may blunt signals from noxious stimuli. In OFA, it may be used as a single bolus dose or an intravenous infusion. [24]

- Dose
  - 30-50 mg/kg (loading); 6-20 mg/kg/h (infusion)
- Pros
  - Anaesthesia-/analgesia-sparing
  - Reduces post-operative opioid requirements
  - Decreased PONV (likely due to less volatile/opioid usage)
  - Decreased post-operative shivering
  - Prolongs neuromuscular blockade (may be disadvantageous)
  - Other uses: anti-arrhythmic, blunting of intubation response, bronchodilation
- Cons
  - May precipitate hypotension
  - Lethargy/sedation [24, 25]

Esmolol

Another, perhaps less intuitive, adjunct is Esmolol – an ultra-short-acting $ß_1$ adrenergic antagonist. Whilst its effects on heart rate and blood pressure are straightforward, the mechanism for its use as an analgesic adjuvant is currently unknown. Nevertheless, it has been shown to be both opioid- and anaesthesia-sparing, as well as reducing post-operative opioid requirements. [26]

- Dose
  - 0.5-1.0 mg/kg (loading); 0.3-6 mg/kg/h (infusion)
- Pros
  - Sympathetic attenuation (can help with blunting intubation response)
  - Possible reduced post-operative pain (mixed results)
- Cons
  - Potential for bradycardia and hypotension
  - Current literature has high heterogeneity and bias [26-28]

Dexamethasone

Another analgesic adjuvant is Dexamethasone, a drug which is already commonly used for its anti-emetic properties, as well as to reduce swelling and discomfort after airway manipulation. It is a steroid that has predominantly glucocorticoid activity, with minimal mineralocorticoid activity. The binding of the drug results in gene transcription and reduced inflammatory mediators, and so its effect as an adjuvant works best with

early administration. Additionally, it enhances and prolongs regional anaesthetic techniques as well, further adding to its value in a multimodal analgesic approach. [29]

- Dose
  - Varies, 8mg is 'typical' adult dose
  - Need at least 0.1 mg/kg for effect as analgesic adjuvant
- Pros
  - Reduced post-operative opioid consumption
  - Reduces rebound pain after regional blocks wear off
  - Decreased fatigue in post-operative period, with improved recovery
- Cons
  - Increase in blood glucose levels
  - Perineal discomfort [29, 30]

Gabapentinoids

Lastly, gabapentinoids are anticonvulsant agents that initially found their analgesic use in chronic pain. Their function as adjuvants is via the antagonism of presynaptic calcium channels in dorsal root ganglion and spinal cord, which prevents the release of excitatory nociceptive transmitters (e.g. substance P). [31] At the time of writing, they are not available in theatre within the South African public healthcare system.

- Dose
  - Gabapentin: 300-1200 mg
  - Pregabalin: 50-300 mg
- Pros
  - Opioid-sparing
  - Anxiolysis
  - Potential prevention of chronic pain and hyperalgesia
- Cons
  - Post-operative sedation
  - May cause significant dizziness [31]

WHEN SHOULD WE USE OFA?

With so many drugs involved in the conducting of an opioid-free anaesthetic, it is of vital importance to understand when OFA should be employed, and if there are factors about a case that may preclude its use.

Indications

At present, there is a paucity of large-scale trials covering opioid-free anaesthesia in general practice, with the bulk of the literature focusing on specific surgical populations. [4] As such, while OFA may be considered in most surgical cases, we cannot make an explicit recommendation regarding routine practice. That said, situations where it has been studied and may be indicated include the following:

- Morbid obesity
- Obstructive sleep apnoea
- Bariatric surgery
- History of PONV
- Oncologic procedures
- Laparoscopic surgery
- History of opioid-use disorders
- Chronic pain or strong concern of opioid-induced hyperalgesia/tolerance [4]

Bariatric Surgery

OFA has been shown to reduce post-operative morphine consumption and improve patient satisfaction in patients undergoing bariatric surgery, whilst not disturbing haemodynamic stability or worsening sedation. [32, 33] Results have not always been uniformly replicated, however, with another study showing that OFA provided no significant difference in opioid consumption 24 hours after bariatric surgery compared to an opioid-based technique. Of note, both the opioid-free and opioid-based groups in this study were given paracetamol, lidocaine, and gabapentin. Additionally, ketamine, whilst only used in the OFA group, was given as a bolus without infusion. [34]

Oncology Surgery

Opioid use has been linked to potential increased cancer recurrence after surgery, but the evidence supporting this is based on pre-clinical in-vitro and in-vivo studies. As of yet, clinical studies have had mixed results, so while there is a theoretical rationale for OFA in this population, a clear recommendation is lacking. [35]

Laparoscopic Surgery

Opioid-free techniques can provide comparable analgesia to opioid-based regimens, whilst reducing PONV by 40% and post-procedural opioid requirements by 6.4mg of morphine/ equivalent. [36] Evidence has also shown non-inferiority in the quality of recovery after laparoscopic hysterectomy, whilst reducing both the incidence and severity of PONV – a notable benefit when the patient sex, type of operation, and surgical are all known risk factors. [37, 38]

Contraindications

Contraindications may be drug-specific (such as an allergy or organ dysfunction precluding the use of a particular class of analgesic), or technique-limiting – in which the clinical context restricts or prevents the use of a number of agents to the point where proceeding with OFA is unlikely to provide appropriate analgesia. Examples of these situations are haemodynamic instability, acute coronary syndromes, severe dysrhythmias, and autonomic dysfunction. [4, 39]

OFA Protocols and Cocktails

Once the decision to perform an opioid-free anaesthetic has been made, one needs to decide on the drug combination that will be utilised.

Unfortunately, while there are many trials with specified regimens of opioid-free anaesthesia, formal evidence-based protocols are lacking – with perhaps the only easily accessible one being an approach described by Mulier from Bruges. The 'OFA5' is the most recent version, although several iterations of this approach have been described since its inception. [40]

The same author later described a single infusion syringe method, known as the 'Mulimix'. [41] Both versions are detailed below.

A third combination is also included that specifically does not utilise gabapentinoids or α-agonists due to non-availability/cost in the current South African public healthcare setting. It must be noted that this is not a protocoled technique, and has rather been extracted from studies conducting OFA without those two classes of drugs.

Bruges 'OFA5' Protocol

- Prepare peri-operative infusion in 1L of crystalloid to run at 1 ml/kg/h
  - Ketamine 50mg (50 µg/kg/h)
  - Magnesium 5g (5 mg/kg/h)
  - Lidocaine/Procaine 1000mg (1 mg/kg/h)
- **Pre-induction**
  - Start peri-operative infusion
  - Dexamethasone 10mg
  - Droperidol 1.25mg
- **Induction**
  - Dexmedetomidine 0.5-1.0µg/kg loading
  - Lidocaine 1mg/kg
  - Magnesium 40 mg/kg
- **Maintenance**
  - Keep volatiles between 0.7-1 MAC and use BIS monitoring
  - Dexmedetomidine infusion 0.5 µg/kg/h if procedure > 2 hours
    - Stop infusion 30 minutes before operation ends
  - Continue peri-operative infusion from above
- **Post-operative analgesia**
  - Give paracetamol and diclofenac before waking patient
  - Continue peri-operative infusion
  - May consider adding Dexmedetomidine 0.1 µg/kg/h to bag [40]

‘Mulimix’ Single Syringe OFA Mixture

- Prepare 50ml OFA syringe containing the following:
  - Dexmedetomidine 50µg
  - Ketamine 50mg
  - Lidocaine 500mg
- Give pre-induction loading dose of Dexmedetomidine 0.25 µg/kg
- Run OFA syringe during induction and maintenance at 0.1 ml/kg/h
  - Consider adjuvants (dexamethasone, droperidol, magnesium)
  - Consider additional 0.5 mg/kg ketamine prior to incision
- Reduce OFA syringe rate to 0.05 ml/kg/h at 15 minutes before finishing
- May continue infusion at reduced rate post-operatively in recovery [41]

OFA without α-Agonists or Gabapentinoids

- Loading dose
  - Ketamine 0.5 mg/kg
  - Lignocaine 1.5 mg/kg
  - Magnesium sulphate 30 mg/kg
- Maintenance infusion
  - Ketamine 0.3 mg/kg/h
  - Lignocaine 1.5 mg/kg/h
  - Magnesium sulphate 10 mg/kg/h
- Ensure use of appropriate adjuvants/simple analgesics
- Consider Esmolol where rapid haemodynamic titration may be desired [17, 27, 42]

LIMITATIONS AND CONCERNS

Regardless of which method is chosen, opioid-free anaesthesia is not without its potential pitfalls – clinical, practical, or systemic – and should prompt consideration as to the feasibility and appropriateness of its use for a given case.

Post-Operative Pain Control

While OFA seems to be able to provide an acceptable level of intra-operative analgesia, its reliance on infusions makes it difficult to translate out of a theatre/high care environment. This leads to a dilemma in remaining opioid-free after an operation, especially given that the longer-acting oral analgesics (i.e. paracetamol and NSAIDs) are unlikely to provide sufficient relief on their own after an extensive procedure. Ultimately, this leads to the requirement of opioids in the post-operative phase. While this is expected and accounted for by the definition of OFA only including the pre- and intra-operative periods, it does re-introduce the potential for experiencing many of the opioid-related side effects that OFA aims to avoid. A counter to this is that many of the agents available for OFA are noted to have an opioid-sparing effect and decrease post-operative opioid requirements, and would thus still limit the extent of opioid-related disadvantages. [17]

Therapeutic Range and Adverse Effects

In addition to being opioid sparing, many of the drugs used for OFA have at least one other non-analgesic effect, such as sedation with Dexmedetomidine and Ketamine. These effects may occur at a close/overlapping dose to that used for analgesia, but may not be desirable in the specific clinical context. At the same time, a certain minimum dose is required to achieve analgesia. This may lead to a relatively narrow therapeutic range, and not allow for significant titration without risking adverse or unwanted effects. [5, 16, 20]

Complexity of Implementation

Current OFA techniques rely on multiple drugs, often given as a continuous infusion. Furthermore, drugs such as Esmolol and Dexmedetomidine can significantly impact the circulatory system and may require frequent titration according to a patient's haemodynamic condition. [18, 26] There may also be a need for extra intravenous lines, more mixing of drugs for infusion, and cognisance of when to give/stop certain agents to prevent impediments like delayed emergence – all of which make opioid-free anaesthesia a more significant mental undertaking than an opioid-based strategy might.

Cost and Resources

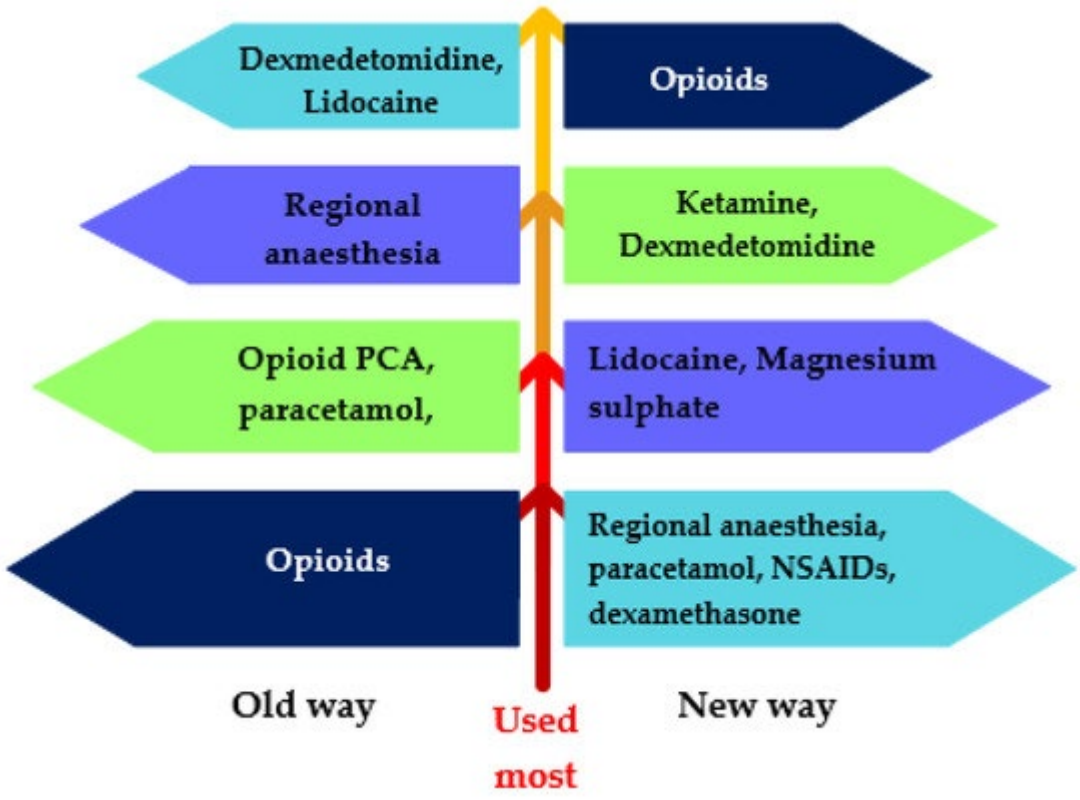
Every drug used is an added expense, as is each piece of equipment (especially those which are single use). This is of critical importance in an environment that is resource-constrained and may not be able to afford the use of OFA on a regular basis. Conversely, the reduction in various post-operative complications and potential for faster recovery may help mitigate costs, but further research is required before an accurate evaluation may be made. [5, 17]

OPIOID-FREE VS OPIOID-SPARING

Opioid-sparing anaesthesia also embraces the multimodal analgesia concept, but with the aim of minimising intra-operative opioid usage – rather than eliminating it completely – so as to still benefit from the excellent analgesic effects that opioids provide. [43] When compared to OFA, opioid-sparing techniques were found to have a similar performance in terms of post-operative pain control and reduction in post-operative opioid requirements, whilst also having a lower risk of intra-operative bradycardia. [44, 45] OFA, on the other hand, offered a superior prevention of PONV, and was also noted to have a shorter time to bowel recovery after laparoscopic cholecystectomy. [45, 46]

Both techniques are changing the approach to intra-operative analgesia, and opioids appear to be undergoing an evolving role from 'default' to 'as needed'. This change is captured in Diagram 2, showing how current multimodal methods may significantly alter our strategy with regards to intra-operative analgesia.

Diagram 2: The potential impact of multimodal analgesia on the anaesthetic approach [47]



CONCLUSION

Opioid-free anaesthesia aims to address multiple factors in peri-operative pain control and quality of recovery after surgery. In a world where the impact of an anaesthetic is taken beyond the operating theatre, OFA presents itself as an enticing prospect – and has shown that it does indeed have merit and is a valid option in the anaesthetist's toolbox.

Its exact role, however, is yet to be determined. Current literature has shown potential scenarios in which OFA may be a strong consideration, but more research is needed before practice-changing recommendations can be made definitively.

Opioid-sparing techniques offer a simpler middle-ground, and deliver many of the same benefits without some of the limitations described for OFA. But perhaps comparing them is a mistake in itself, and we should instead consider opioid-free to fall within the opioid-sparing spectrum – with the focus on post-operative goals and the extent to which opioid-usage may affect them. Throughout all of this, care should remain patient-centred, and the pros of each decision weighed against their cons.

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