Opioid-Free Anaesthesia

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Published 14 December 2021

KEY POINTS

- Opioid-based anaesthesia has well-recognized side effects.
- Opioid-free anaesthesia has emerged as a feasible, effective alternative to avoid opioid-related side effects and is advantageous in a selected group of patients.
- Increasing evidence shows a multimodal approach with nonopioid analgesics may improve outcomes following surgery in selected high-risk groups such as those with morbid obesity or obstructive sleep apnoea.

INTRODUCTION

Before the advent of opioids, the goals of general anaesthesia—hypnosis, immobility, and analgesia—were achieved with high doses of hypnotics or inhalational agents. This technique often caused severe haemodynamic instability. The introduction of opioids and balanced anaesthesia offered better haemodynamic stability by allowing a reduction in doses of other agents. Thus, opioids became popular as they improved the outcome after anaesthesia and surgery. Opioid-based anaesthesia, however, has well-recognized side effects based on its receptor targets as well as its complex effect on the immune system. Furthermore, the ongoing opioid crisis highlights the importance of good opioid prescribing stewardship. Recently there has been a move towards non–opioid-based anaesthesia to avoid opioid-related adverse effects. This tutorial will review the reasoning for opioid-free anaesthesia (OFA) and discuss the advantages and disadvantages of such a technique.

WHY OFA?

- Use of OFA reduces common side effects of μ, δ, and κ activation such as sedation, dysphoria, delirium, constipation, urinary retention, and postoperative nausea and vomiting.
- OFA reduces the chances of life-threatening side effects such as respiratory depression and airway obstruction.
- Use of OFA promotes rapid recovery. Current Enhanced Recovery After Surgery (ERAS) protocols recommend reducing perioperative opioid usage for an uncomplicated and rapid recovery.[1] Opioid-related side effects prolong the hospital length of stay and increase the cost of medical care.[2]
- Postoperative hyperalgesia and tolerance due to neuroadaptation increases the requirement for long-acting opioids, and is more prevalent with the newer short-acting opioids, like remifentanil.[3]
- Surgery and anaesthesia have a complex effect on immunity. Opioid anaesthesia is reported to inhibit both cellular and humoral immunity, which can lead to early cancer recurrence.[4]

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- OFA use responds to a public health crisis. Patients leaving the hospital with an opioid prescription for postoperative analgesia are at a higher risk for dependence. The epidemic use of opioids in the United States has caused significant morbidity and mortality with an estimated 2 million dependent users and another 12 million misusers reported in 2015.[5]

These compelling reasons have made clinicians look to clinically feasible alternatives to reduce or avoid perioperative opioids. They have found that by using nonopioid analgesic adjuvants and regional analgesia, perioperative opioid usage can be reduced to almost zero.

PAIN PERCEPTION UNDER ANAESTHESIA

The concept of pain perception under anaesthesia has been questioned recently. In an anaesthetized patient, it is more precise to use the term nociception, as pain requires the patient to be conscious to perceive it. In a conscious person, a nociceptive stimulus will result in haemodynamic (tachycardia and hypertension), ventilatory (hyperventilation), and behavioural (withdrawal) responses, in addition to discomfort. Under adequate hypnosis (BIS 40-60) and paralysis, tachycardia and hypertension are the usual clinical indicators of inadequate antinociception. Thus, our main intraoperative goal is haemodynamic stability.[6] The connection between ascending pain pathways with autonomic neurons in the vasomotor centre of the medulla forms the basis of a rise in heart rate and blood pressure with nociceptive stimulus.

The adequate control of haemodynamic responses during anaesthesia does not guarantee that a patient will emerge from anaesthesia without pain, so it is equally important to address nociceptive pathways as well as the autonomic response. Nociception can potentially induce central nervous system changes including sensitization. This is the rationale for using a multimodal antinociceptive approach during OFA.

Monitoring Antinociception Under Anaesthesia

It is difficult to monitor the adequacy of antinociception under anaesthesia. Depth of anaesthesia does not necessarily correlate with the adequacy of antinociception. To solve this issue, surrogate indices which are derived from the autonomic system rather than electroencephalogram are being studied. Current examples include analgesia-nociception index, cardiovascular depth of analgesia, or surgical pleth index. They attempt to monitor antinociception using the autonomic nervous index. [6]The analgesia-nociception index is a cardiac vagal activity monitor based on heart rate variability. Cardiovascular depth of analgesia uses electrocardiogram and noninvasive blood pressure recordings but is of limited use in patients with dysrhythmias or pacemakers and with vasoactive drugs. The surgical pleth index is derived from the photoplethysmographic waveform and R-R interval changes but is inaccurate in low intravascular volume states. Other examples include pupillary measurements. Experimentally they are found to be more sensitive in monitoring nociceptive stimulus, as pupillary dilatation under anaesthesia is dependent upon the parasympathetic system. Pupillary dilatation precedes any haemodynamic changes with nociceptive stimulus under anaesthesia but is difficult to use as a continuous monitor because of the associated risk of corneal infection or trauma. A multi-parameter approach utilizing combinations of the above parameters to create compound indices like the nociception level index, may be superior in terms of sensitivity and specificity as an index of antinociception.[7]

IS IT POSSIBLE TO AVOID INTRAOPERATIVE OPIOIDS?

Haemodynamic stability with opioid analgesia is achieved by blocking enkephalins, some of the many transmitters within pain pathways. Several other transmitters like glutamate, noradrenaline, gama-aminobutyric acid, and serotonin are also involved in heart rate and blood pressure regulation, which opens the possibility of using other pharmacological agents acting on ascending or descending pain pathways. Intraoperative nonopioid analgesics and adjuvants like lignocaine, α_2 agonists, beta-blockers, magnesium sulphate ($MgSO_4$), ketamine, dexamethasone, gabapentinoids, nonsteroidal anti-inflammatory agents, and paracetamol (acetaminophen) are found to suppress the rise in heart rate and blood pressure. Sympathetic attenuation can be achieved by the direct action of α_2 agonists or beta-blockers and indirectly with $MgSO_4$ or lignocaine. Since perioperative pain differs largely in terms of the character of pain, individual sensitivity, and possible site of modification on pain pathways, it is reasonable to assert that one type of analgesic will not be sufficient for all triggers of nociception. A multimodal approach targeting various points of the pain pathways with 2 or more nonopioid adjuvants should give additive or synergistic effects, allowing a reduction in the side effects of each whilst maintaining haemodynamic stability.

OPIOID-FREE ANAESTHESIA

A multimodal antinociceptive approach is utilised to achieve OFA. The nonopioid analgesic adjuvants that have been used in OFA include lignocaine, α_2 agonists, beta-blockers, $MgSO_4$, ketamine, dexamethasone, gabapentinoids, nonsteroidal anti-

inflammatory agents, and paracetamol (acetaminophen). Various combinations and doses of these adjuvants have been trialled worldwide as part of an OFA regimen.[8]

α_2 Agonists

The α_2 agonists are ideal agents for an OFA regime because of their favourable pharmacological features including sedation, hypnosis, anxiolysis, sympatholysis, and analgesia. A meta-analysis demonstrated that perioperative use of systemic α_2 agonists resulted in decreased postoperative pain intensity and opioid consumption without prolongation of recovery time.[9]Dexmedetomidine preserves airway patency and the normal sleep architecture. It also has bronchodilator properties. It lacks any of the common side effects of opioids such as respiratory depression, urinary retention, pruritus, ileus, or postoperative nausea and vomiting and is reported to decrease postoperative opioid requirement by $>$50%.[10] It offers better heart rate control perioperatively and can cause a transient rise in blood pressure followed by a slight reduction of up to 10% of baseline.

Lignocaine (Lidocaine)

Lignocaine (lidocaine) has analgesic, anti-inflammatory, opioid-sparing effects, and coanaesthesia properties. Downregulation of neutrophil degranulation is thought to be the primary mechanism behind the antinociceptive effect of lignocaine rather than just its sodium channel blocking property. Several randomised controlled trials and systematic reviews have established that perioperative intravenous lignocaine infusion significantly decreased the anaesthetic and opioid requirement, reduced the incidence of postoperative nausea and vomiting with a faster return of bowel function, and improved quality of recovery.[11]

Ketamine

Ketamine is now known to have more mechanisms of action than just an N-methyl-D-aspartate receptor blocker. It decreases opioid requirements and the incidence of chronic postsurgical pain and is found to be effective even in patients with a high opioid requirement or opioid refractory pain. Ketamine and magnesium can prevent haemodynamic variability intraoperatively and this combination can be seen as complementary to produce analgesia and haemodynamic stability.[12]

Magnesium

Magnesium is also an N-methyl-D-aspartate receptor antagonist in addition to its effects on calcium influx. The anti-inflammatory and opioid-sparing effects make it a popular component of OFA. It is extensively used for perioperative analgesia in a dose of 30- to 50-mg/kg intravascular bolus followed by a 10- to 15-mg/kg/h infusion.[12] It does have some adverse effects, including potentiation of neuromuscular blockers and hypnotics. It can also cause hypotension secondary to vasodilatation, which should be borne in mind when it is used in combination with α_2 agonists and propofol.

Beta-Blockers

Beta-blockers are frequently used to attenuate the unwanted haemodynamic responses during surgery and can be used as an adjunct to preoperative analgesia Intraoperative esmolol is reported to decrease the intraoperative and postoperative opioid requirement, facilitating earlier discharge.[13] However, the exact mechanism of opioid-sparing effect of esmolol is not known as it does not possess antinociceptive properties.

Others

Gabapentinoids (gabapentin and pregabalin) are indirect calcium channel blockers. They are an analgesic, and commonly used for neuropathic pain. Their main disadvantage is excess postoperative sedation in some patients.

Dexamethasone has analgesic properties in doses more than 100 μg/kg in addition to its antiemetic and anti-inflammatory effects.

Paracetamol (acetaminophen) has a very good safety profile and is found to reduce pain intensity and opioid requirement when used as an adjuvant. It is recommended that paracetamol be administered regularly as part of a multimodal regimen.

Regional Analgesia

Regional analgesic techniques including peripheral nerve blocks, facial plane blocks, paravertebral and paravertebral variant blocks, and neuraxial blocks have been incorporated along with multimodal analgesic protocols. For example, the addition of

Transversus Abdominis Plane (TAP) blocks to ERAS protocols has been found to decrease postoperative opioid requirements and hospital stay after abdominal surgery.[2] Various other facial plane blocks such as serratus anterior, erector spinae, and quadratus lumborum blocks are now gaining greater interest as perioperative analgesic tools combined with balanced general anaesthesia to avoid opioids. Peripheral nerve blocks or simple wound site infiltration with local anaesthetics are also highly effective for perioperative analgesia.

ADVANTAGES OF OFA

OFA, which avoids intraoperative opioids by any route, has specific advantages and is indicated in a selected group of patients such as the obese, those with obstructive sleep apnoea syndrome (OSAS), chronic obstructive pulmonary disease, asthma, acute or chronic opioid addiction, or chronic regional pain syndromes, as well as those undergoing cancer surgeries and for patients in an ERAS pathway.

Morbid Obesity and OSAS

The use of intraoperative opioids and OSAS are recognised risk factors for the development of postoperative hypercapnic respiratory failure in morbid obesity. The unique problems associated with morbid obesity such as decreased respiratory reserve, impaired respiratory muscle function, increased oxygen requirement, and associated OSAS and pulmonary hypertension make these patients more vulnerable to opioid side effects. Avoiding respiratory depression and obstructed breathing is of paramount importance in obesity, hence the need to avoid opioids. The OFA movement began in obese patients coming for bariatric surgery. From studies on morbidly obese patients for bariatric surgery, it is thought that dexmedetomidine is an ideal agent in such patient groups. Dexmedetomidine preserves the normal sleep architecture and airway patency, thus ensuring patient safety and facilitating early discharge in obese patients.[1]

Cancer Surgery

The intraoperative period is the most crucial time during which surgical stress, anaesthesia, and many other perioperative factors adversely affect cancer prognosis by stimulation of the hypothalamo-pituitary axis and sympathetic nervous system, and the release of mediators that cause immunosuppression. These mediators promote the proliferation of residual tumour cells which get liberated and thus metastasise, causing recurrence. Perioperative uses of large doses of opioids are found to be associated with early recurrence in patients undergoing primary cancer surgery.[14] Opioids are found to inhibit both cellular and humoral immunity, increase angiogenesis, and stimulate tumour cell proliferation in vitro.[4] They suppress natural killer cells, cytokine and antibody production, and phagocytic activity. Perioperative natural killer cell activity has a crucial role in determining the outcome after cancer surgery as they are the primary defence against cancer cells. Opioid-induced natural killer cell suppression in humans was found to be prolonged in the postoperative period. It is difficult to predict the long-term effects of anaesthetic techniques or agents in cancer surgery with the limited available evidence at present. Many associated confounding variables like tumour cell biology, allogenic blood transfusion, and surgical technique make it extremely difficult to draw conclusions from the current evidence about opioid-induced cancer metastasis. However, since opioid analgesics are reported to have a deleterious effect, even the limited advantages of opioid avoidance could be of great help to a cancer patient. A beneficial effect of opioid avoidance is reported in colorectal and breast cancer surgery. Large outcome studies are needed to establish any definite advantages of OFA and regional anaesthesia in other onco-surgeries.

Fast-Tracking ERAS

Opioid minimization is one of the cornerstones of an ERAS protocol. Opioid-associated adverse effects prevent smooth and rapid emergence and prolong the hospital length of stay. A multimodal approach would provide good quality analgesia and facilitate early discharge in day-surgery settings. In a recent systematic review and meta-analysis of 23 randomised controlled trials involving 1304 patients, the authors concluded that opioid-based anaesthesia does not reduce postoperative pain or opioid requirement, but it is associated with a higher incidence of postoperative nausea and vomiting, which can delay postoperative recovery and discharge.[15]

DISADVANTAGES OF OFA

The component drugs of an OFA regime may have specific side effects. The individual components of a multimodal OFA regime should be selected carefully based on patient characteristics, individual familiarity, availability, and any adverse effects that could occur. The α_2 agonists should be used with extreme caution in patients with cardiovascular disease like atrio-ventricular blocks and in elderly patients on beta-blockers. Other relative contraindications to OFA include critical coronary stenosis or acute coronary syndrome, uncorrected hypovolemic shock, and autonomic

dysfunction. The potential for awareness exists if inadequate hypnotic is used. There is a definite learning curve to OFA and our collective experience is limited compared with the use of 'balanced' techniques that include opioids.

SUMMARY

The inherent problems of opioid-based analgesia have moved clinicians to explore new horizons of multimodal nonopioid analgesics. It may be difficult to avoid perioperative opioids completely in all cases, but the addition of multimodal nonopioid analgesics and regional analgesic techniques might help to reduce opioid requirements. Multimodal OFA may now be considered to be the primary choice wherever possible, and opioids can be reserved for rescue analgesic use. Even if indicated, perioperative opioids should be limited to the lowest possible dose.

In conclusion, OFA has now emerged as a feasible and safe alternative to the conventional opioid-based general anaesthesia in selected groups of patients. The risk-benefit ratio of OFA should be considered on an individual basis. The various OFA protocols trialled worldwide need refinement and potential interactions of the individual components need to be explored further. Finding a reliable monitoring tool for the adequacy of intraoperative antinociception is currently being explored.

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