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OPIOID FREE ANAESTHESIA

A de Castro

Moderator: L Cronje

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI

School of Clinical Medicine
Discipline of Anaesthesiology and Critical Care

CONTENTS

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INTRODUCTION

Pain is an important contributor to post-operative distress[1] and is reported as the primary concern for 56% of surgical patients.[2] Seventy five percent of surgical patients report inadequate pain management postoperatively and this can lead to prolonged hospital stays, unnecessary readmissions, increased morbidity and increased healthcare costs.[1] Uncontrolled severe acute pain can cause permanent conformation in spinal cord pathways and cause debilitating chronic pain syndromes.

HISTORY OF OPIOIDS IN ANAESTHESIA

Dr. Horace Wells administered the first anaesthetic using nitrous oxide in 1845 and was quickly followed by his colleague, Dr. William TG Morton with the use of ether in 1846. It was considered a revolution in medicine.[2]

The goal of general anaesthesia is to provide hypnosis, analgesia and relaxation. Before the introduction of opioids in the 1960s, deep inhalational anaesthesia or high dose hypnotics were used to achieve hypnosis and immobility, and to suppress the sympathetic response to pain. These high doses would often lead to hemodynamic instability.[3]

The introduction of opioids and the advent of balanced anaesthesia was a much needed solution to this problem. The discovery of opioids was important because older hypnotic agents were strong cardiovascular depressant agents. Administration of high doses of opioids allowed the reduction of hypnotics and provided suppression of the sympathetic system thereby maintaining hemodynamic stability.[3]

Since then intra-operative opioid use has become standard practice. Opioid cardiac anaesthesia has been common practice since the 1980s[4] and opioids are often used to blunt the intubation response. Fentanyl is commonly used to attenuate elevated BP and HR attributable to pain[4] and short-acting opioids are considered to be the preferred method for intense painful stimuli but still ensuring rapid recovery without increasing side-effects.[5] Total intravenous anaesthesia (TIVA) with the use of an opioid is also commonly used to avoid the postoperative nausea and vomiting (PONV) associated with inhalational agents.[3]

Opioids are successful as they block ascending nociceptive stimuli thereby reducing the dose of hypnotics needed (“mac sparing effect of opioids”) and facilitate hemodynamic stability, reduce cardiac output without reducing coronary perfusion and block respiration thereby facilitating ventilation.[3]

IS A NEW APPROACH INDICATED?

Surgical anaesthesia aims to provide amnesia, analgesia, control of autonomic effects and rapid emergence. A stress free anaesthetic is required and the availability of opioids were the ideal agents to achieve these needs in the past.[3] The availability of newer, less cardiovascular suppressant anaesthetic drugs forms the basis of the opioid free anaesthesia "movement": Are opioids still needed to achieve these goals and are outcomes the outcome perhaps better without them?[3]

A new approach to anaesthesia has thus been suggested and should include hypnosis with amnesia, sympathetic stability to protect organs and provide sufficient tissue perfusion, and muscle relaxation.[3]

INTRA-OPERATIVE PAIN

The International Association for the Study of Pain (AISP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".[6]

This begs the question: Can an unconscious patient experience pain?

Nociception, however, is the processing of noxious or potentially noxious stimuli. The anaesthetized patient is not able to report nociception as pain, but these processes are still ongoing during hypnosis. Objective indices of nociception is used to assess 'pain' and its attenuation by analgesics.[7] Indirect signs of autonomic nervous system responses are most commonly used and objective scoring systems to measure intraoperative nociception has been developed to measure intra-operative pain. The 'Analgoscore' is based on blood pressure and heart rate variability and has been used to measure pain control with remifentanil. Target values for mean arterial pressure (MAP) and heart rate (HR) are defined by the anaesthetists. A change from these values are used to determine a score according to Table 1 and is defined on a scale ranging from 'too profound analgesia' to 'insufficient analgesia'.[8]

TABLE I.
RULES FOR SCORE DETERMINATION

HR \ MAP	<20%	<15%	<10%	<5%	MAP	>5%	>10%	>15%	>20%
<35%	-9	-8	-6	-5	-4	Vagal Reaction			
<25%	-8	-7	-5	-4	-3				
<15%	-6	-5	-4	-3	-2				
<10%	-5	-4	-3	-1	-1				
HR	-4	-3	-2	-1	0	1	2	3	4
>10%	Hypotension caused by volume depletion				1	1	3	4	5
>15%					2	3	4	5	6
>25%					3	4	6	7	8
>35%					4	5	6	8	9

MAP = mean arterial pressure; HR = heart rate

The anesthetized patient pain scale (APSS) is another novel model to assess intra-operative pain. It consists of physiological and behavioural indicators that include blood pressure (BP), HR, respiratory rate (RR), facial expression, muscle tension and body movements. The latter three would be completely diminished by muscle relaxation. Each item is given a score from 1 to 3 and the intensity of pain is indicated by the final score.[2] The biggest flaw in these types of methods is the fact that many factors can be responsible for changes in MAP and HR during anaesthesia and it simply indicates the level of sympathetic activation and autonomic response. As such, it stands to reason that fentanyl will normalize vital signs, as it blocks these autonomic responses, a similar effect to that of any sympatholytic e.g. Esmolol.[4]

It is therefore possible that "being pain free" is only important post-operatively when patients are awake,[3] thus a new approach to anaesthesia has been suggested. What seems to be important is sympathetic stability and avoidance of detrimental effects of nociception rather than "analgesia". This may be achieved by control of the sympathetic and hormonal stress response which suppresses inappropriate inflammatory responses and avoid suppression of the immunological response that would lead to decreased wound healing.

WHY PRACTICE OPIOID FREE ANAESTHESIA (OFA)?

Opioids are still the ideal agents to achieve these "new goals", so why the big fuss to avoid it?

1. Opioid-related side-effects

Currently opioids are the mainstay of peri-operative pain management but the use of opioids, even though effective, can result in a myriad of perioperative side-effects. These side-effects are one of the main reasons that opioids are not included, or minimized in ERAS protocols. They prevent smooth postoperative recovery[9] and can delay hospital discharge.[10] The incidence of opioid-related adverse events in surgical patients after being treated with opioids was reported as 2.67% in one study and were related to increased duration of admission as well as health care costs, although there was no effect on mortality.[11]

Commonly experienced complications or side-effects of opioid use include:

- Delayed emergence, somnolence, dizziness
- GI side-effects e.g. ileus and constipation, nausea and vomiting
- Coma and death
- Respiratory depression
- Pruritis
- Urinary retention
- Tolerance by desensitization
- Reduced cardiac output
- Short duration of central muscle stiffness

2. Acute tolerance/hyperalgesia

Potent opioids may be rapidly eliminated or lead to acute tolerance which may paradoxically increase postoperative pain.[10] This has been labeled the opioid paradox: The more opioids that is given intra-operatively, the more is needed postoperatively and the higher the pain scores will be.[3] Prolonged exposure to opioids shifts the dose-

response curve in such a way that larger doses of opioids are needed over time to render the same level of analgesia. This is called opioid tolerance.[12] Some authors suggest that if no opioids are given intra-operatively, less opioids will be needed postoperatively as tolerance has not destroyed the mu-receptor system yet.[3] Hyperalgesia is caused by exposure to opioids leading to a state of nociceptive hypersensitization. It is a phenomenon seen in opioid treated patients who demonstrate an increased sensitivity to nociceptive stimuli.[12] Hyperalgesia and opioid tolerance is greatest with the use of short-acting lipophilic or synthetic opiates especially remifentanil but has also been described following morphine,[4] fentanyl[13,14] and sufentanil[4] use.

Patients receiving high doses of fentanyl during surgery consistently required higher doses of opioids during the postoperative period than those receiving lower doses[13]. A systematic review of fentanyl looked at six randomised controlled trials and found two trials opposed to and four trials in support of the occurrence of fentanyl induced hyperalgesia.[14] Patients receiving fentanyl intraoperatively consumed 250% more opioids post-operatively compared to a group that received intravenous esmolol.[5] A direct correlation has been demonstrated between the amount of intraoperative sufentanil received and the severity of pain in the recovery room.[15]

In general, postoperative patients appear comfortable after a narcotic general anaesthetic and often report little pain in the recovery room but as anaesthetists we are often unaware of hyperalgesia during the subsequent 1 – 4days.[4] Opioids provide an initial analgesic effect but development of acute tolerance can lead to an increased need for analgesics and opioids may therefor not be particularly effective in controlling postoperative pain.[16]

It has been postulated that NMDA receptor antagonists may prevent acute tolerance or long-lasting hyperalgesia.[17] Magnesium seems to lower the incidence of remifentanil induced hyperalgesia. Adding magnesium sulphate to a remifentanil infusion for major lumbar surgery led to lower postoperative pain scores and opioid use.[18] Ketamine significantly reduced morphine requirements in opioid-dependent patients undergoing lumbar surgery for chronic back pain. This effect was seen until 48hours postoperatively.[7]

DRUGS AVAILABLE TO REDUCE OPIOID REQUIREMENTS

So, it seems that what is needed is blocking of the sympathetic system. Opioids were the ideal agents to block this sympathetic response in the past. But today we have other drugs available for this purpose. Direct central or peripheral sympathetic block can be achieved with the use of clonidine, dexmedetomidine and beta-blockers. An indirect block can be achieved by the use of calcium channel blockers, lignocaine, $MgSO_4$ and inhalational agents.

Evidence indicates that multimodal pain management is the best way to reduce opioid consumption. Multimodal analgesia includes local anaesthetic as well as systemic drugs and aim to reduce the dose of any single agent thereby reducing the potential for adverse effects. Avoiding opioids during anaesthesia is possible without hemodynamic instability. A stable anaesthetic with a multimodal approach of sympatholytic drugs and non-opioid analgesics can be achieved. This can reduce and frequently avoid use of any opioid postoperatively as well.[3]

Regional anaesthesia can completely obviate the need for opioids in certain situations. This is certainly the biggest weapon in our arsenal in the fight against opioids but for the purposes of this booklet, the use of regional anaesthesia will not be delved into. The second approach is to either avoid all opioids during general anaesthesia or use adjuvant agents for their opioid sparing effect. This can be achieved by using drugs that block the autonomic nervous system's reaction to painful stimuli. This method was first described with high doses of alpha-2 agonists like clonidine and dexmedetomidine. The blocking of sympathetic nervous system effects are needed during anaesthesia and is classically achieved with high doses of opioids. The use of alpha-2 agonists would therefor replace opioids for this indication. However, this can cause high levels of sedation and for this reason multimodal methods are proposed in order to decrease the high incidence of postoperative sedation.[19]

The use of non-opioid analgesics after opioid-free anaesthesia has been found to be effective for postoperative pain. Local wound infiltration with long-acting local anaesthetics can improve postoperative pain control. With minimally invasive surgical techniques, surgical trauma can be minimised and the use of anti-inflammatory agents can improve quality of recovery and decrease postoperative pain.[19] Non-opioid analgesics like NSAIDs and paracetamol are often employed peri-operatively. Additionally low-dose dexmedetomidine or clonidine can also be used. Similarly lignocaine, magnesium and ketamine can also be employed to improve the autonomic block as well as postoperative analgesia.[19]

Different drugs will now be considered in more detail.

Alpha-2 agonists

The use of alpha-2 adrenoreceptor agonists as analgesics and sedatives were first studied in veterinary medicine. Clonidine was first introduced as a potent nasal decongestant in the 1960s. It has been used as an antihypertensive, sedative and analgesic.[20] Clonidine has been used consistently since the late 1980s[4] whereas the use of dexmedetomidine has been increasing over the last 10 years. Alpha-2 agonists have pharmacological characteristics that make them suitable as part of a multimodal analgesic regime. These include sedation, hypnosis, anxiolysis, sympatholysis and analgesia.

The administration of a dexmedetomidine bolus initially results in activation of alpha-2 receptors on vascular smooth muscle. This causes initial vasoconstriction, and a transient increased BP and reflex bradycardia can be seen. Following this a more gradual central effect is seen which causes sedation and a decrease in sympathetic outflow. This could be the cause of reduced MAP and sedation seen postoperatively.[21] The antinociceptive effect of the alpha-2 agonists is thought to be secondary to the stimulation of a2-adreno-receptors located in the CNS and spinal cord. Several studies have demonstrated the effect of neuraxial alpha-2 agonists on post-operative pain but also on neuropathic and cancer pain.[22]

A recent meta-analysis of 30 randomised controlled trials demonstrated that both clonidine and dexmedetomidine results in 24hrs of analgesia. During this time the opioid consumption and pain scores were reduced. Decreased PONV was reported in the first 8hours and recovery times were not significantly prolonged. However the use of alpha-2 agonists was associated with increased sedation, hypotension and bradycardia. This resulted in an increased need for atropine, glycopyrollate or vasopressors. Anaesthetic requirements could be reduced by 25% which ameliorated these negative effects and

there was no increase in the incidence of major adverse outcomes e.g. MI or admission to ICU. These were however small sized studies with a variety of drug regimens and surgery types being investigated.[22]

Following radical abdominal surgery, morphine requirements were reduced by 50% by adding oral and transdermal clonidine to the premedication.[23] Postoperative clonidine added to morphine demonstrated reduced pain scores and PONV in patients undergoing lower abdominal surgery, but no difference in overall opioid requirements were shown.[24,25] Intra-operative use of dexmedetomine reduces morphine use postoperatively[26] and use in the postoperative period can decrease pain comparable to IV oxycodone.[27]

Intraoperative use of dexmedetomidine in lew of morphine significantly reduced postoperative morphine use. A slower HR but similar MAP, RR, sedation, nausea and time to discharge was demonstrated.[21] Similarly the use of dexmedetomidine compared with fentanyl in patients undergoing tonsillectomy prolonged the postoperative opioid free interval. However the length of stay in the recovery room was increased due to significant sedation.[28]
Opioid free analgesia was achieved in a patient with opioid-induced delirium undergoing hemicolectomy. Successful postoperative analgesia was obtained with dexmedetomidine and clonidine administered via various routes.[20]

Adverse drug reactions of alpha-2 agonists may prevent their routine use. Bradycardia and arterial hypotension has been described but it is not associated with respiratory depression regardless of the deep level of sedation. For clinical decision-making, the beneficial effects should be weighed against the increased risk of hypotension and bradycardia.[22] Various doses and regimes are described in the literature. One regime suggests the infusion can be started at 0.4mcg/kg/hr and then reduced to 0.2mcg/kg/hr by the end of the operation. This infusion can be continued in the postoperative period.[29]

Lignocaine

As a sodium channel blocker, lignocaine provides excellent pain relief when given intravenously.[29] IV lignocaine has been shown to have analgesic, anti-hyperalgesic and anti-inflammatory effects.[30] It is considered to be safe and has significant advantages such as decreased intraoperative anaesthetic requirements, as well as faster return of bowel function and decreased duration of hospital stay.[30]

Perioperative infusions of lignocaine has been associated with better postoperative pain control at rest, during cough and during movement at 6hours. It reduces opioid requirement with a reduction in opioid side-effects. Faster recovery from ileus and faster return of bowel function (>24hours earlier) demonstrates a significant benefit after abdominal surgery. Total length of hospital stay is decreased by 1 day. Nausea and vomiting is also reported to be reduced.[31,32] Postoperative quality of recovery is improved with a clear benefit in the outpatient setting, demonstrating less opioid requirements, faster discharge and decreased PONV.[33]

A Cochrane review of intra-operative IV lignocaine found reduction of postoperative pain at 1-4hours and at 24hours but not at 48hours. This reduction in pain was most pronounced in laparoscopic and open abdominal surgery. Beneficial effect on gastrointestinal recovery including time to first flatus and first bowel movement and risk of paralytic ileus was demonstrated. Positive effects on length of hospital stay, PONV and opioid requirements

were also shown. There was limited data on adverse effects e.g. death, arrhythmias or lignocaine toxicity.[9]

A systematic review of 16 randomised controlled trials showed significant reductions in postoperative pain and opioid use in open and laparoscopic abdominal and ambulatory surgery. Pain scores were reduced at rest, with cough and with movement for up to 2 days and opioid use was reduced by 85%. Intraoperative anaesthetic requirements were reduced. Earlier return of bowel function, as well as shorter duration of hospital stay was found. No effect was demonstrated on postoperative analgesia for tonsillectomy, total hip arthroplasty or CABG.[34]

Lignocaine combined with dexmedetomidine has successfully been used in opioid free anaesthesia for laparoscopic cholecystectomy. This significantly reduced postoperative opioid consumption for the first 6 hours and need for ondansetron was also reduced. Lignocaine and dexmedetomidine was not continued into the postoperative period but both groups were treated with fentanyl. The authors speculate that opioid tolerance could account for the comparable need for opioids at 6 hours. Could the positive effects have been prolonged if an opioid free technique was continued postoperatively?[30] A general protocol of 1 – 1.5mg/kg bolus with 2-3mg/min infusion ending in theatre or early in recovery has been suggested.[31] Alternatively a loading dose of 1-2mg/kg followed by an infusion of 1-2mg/kg/hr has been shown to be safe.[29]

Esmolol

Esmolol is an ultra-short acting cardioselective $beta_1$ adrenergic receptor antagonist that is rapidly hydrolyzed by red blood cell esterases. It has a short clinical duration of effect of about 9min.[4] The benefits of beta-blockers in cardiovascular diseases are well established and it can be targeted to attenuate unwanted autonomic responses.[5] It has analgesic effects and benefits beyond its beta-blocking qualities[4] and has been suggested as an alternative to intraoperative opioids.[5]

Esmolol has been shown to facilitate the fast-track protocol and result in earlier discharge in outpatient surgery.[5] Anaesthetic requirements have been reduced, as well as perioperative opioid use and incidence of PONV; thereby leading to earlier discharge and increased global patient satisfaction.[1]

Patients receiving intraoperative esmolol infusion vs intermittent fentanyl or continuous remifentanil infusions showed dramatically lower consumption of opioids in recovery and a 50% decrease in PONV and antiemetic use, compared with patients receiving intraoperative narcotics.[5] Intraoperative esmolol infusion for gynaecologic laparoscopic surgery resulted in lower incidence of PONV, earlier discharge, decreased need for postoperative opioids and faster time to discharge.[35,36] Chia et al used fentanyl at 3ug/kg followed by an infusion of esmolol in women undergoing TAH. Postoperative use of morphine was significantly reduced for the first 3 days postoperatively. No significant difference in side-effects were seen.[37] When compared to a remifentanil-ketamine combination for laparoscopic cholecystectomy, esmolol decreased postoperative pain scores and morphine consumption. Anaesthetic requirements was however increased and PONV was similar in both groups.[38]

Contra-indications to the use of esmolol include bradycardia, heart block, cardiogenic shock and overt heart failure. Caution should be used in diabetes and bronchospastic disease.[1]

Magnesium

Nociceptive stimuli activate NMDA receptors causing calcium entry into the cell and triggering central sensitization.[18] NMDA receptors control ion channels and depolarization of 2nd order neurons.[4] Magnesium acts as a non-competitive antagonist of NMDA glutamate receptors. It leads to a voltage-dependent block of NMDA receptors by blocking entry of calcium and sodium into the cell (the ketamine receptor prevents efflux of potassium). This prevents depolarization and transmission of pain signals.[4]

The effect of magnesium on postoperative pain have been investigated since the 1990's.[18] Results have been conflicting. A systematic review did not provide convincing evidence of favorable effects of perioperative magnesium administration. Of 14 RCTs reviewed, postoperative analgesic requirements were significantly reduced in 8 trials, showed no effect in 5 and were increased in 1 trial. Most of the trials in this review were small.[39]

IV magnesium administration concurrently with spinal anaesthesia improves postoperative analgesia. Magnesium sulphate administered as a bolus of 50mg/kg for 15min and then 15mg/kg/hr by continuous infusion until the end of surgery significantly reduced postoperative pain scores and opioid consumption without affecting onset or recovery from spinal anaesthesia.[40,41]

Lower pain scores were reported in the first 48hours in groups receiving magnesium during gynaecological surgery. Intra-operative requirement of neuromuscular blockade was reduced and decreased postoperative pain and PONV was reported for >24hrs.[42,43] Similarly, intra-operative and post-operative analgesic requirements were reduced in arthroscopic knee and ophthalmic surgery.[18] Magnesium included in a multimodal analgesic regime for obese patients undergoing gastric bypass surgery resulted in postoperative pain relief comparable to fentanyl use with less adverse effects.[44]

However other studies could not demonstrate a beneficial effect.[45] Magnesium 50mg/kg IV did not produce opioid-sparing effects after open cholecystectomy. Even though better pain relief and comfort was reported in the first postoperative hour, significant morphine requirement was not reduced. It did however result in better quality of sleep postoperatively without any significant side-effects.[46] Following hysterectomy, decreased analgesic use, reduced discomfort and better sleep quality have been found by some investigators but others failed to demonstrate any positive effect.[4] Given as a premedication, 3-4g bolus over 5min followed by a 1-2g/hr infusion, demonstrated effective blunting of the sympathetic response to laryngoscopy and intubation.[4]

Magnesium seems to lower the incidence of remifentanil induced hyperalgesia. In a study by Levaux et. al. adding magnesium sulphate to a remifentanil infusion for major lumbar surgery led to lower postoperative opioid use and pain scores.[18]

The intra-operative dose of magnesium has not been well documented but most studies suggest a plasma level of 2 – 3mmol/l.[29] A bolus dose of 50mg/kg given over 30min has already been reported in several studies to have no significant side effects. A dose of 10mg/kg/hr is quoted by other studies.[19] In order to inhibit central sensitization, it has been suggested that NMDA receptor antagonists should be given prior to surgical stimulation.[4] Caution should be exercised in patients with renal impairment as magnesium is exclusively excreted by the kidneys.[4]

Ketamine

Ketamine is a unique intravenous anaesthetic with analgesic properties. It fell into disfavor in the late 1980s because of its side-effect profile. Ketamine in small doses of 0.1-0.2mg/kg appear to have an opioid-sparing effect with greater patient and physician acceptance because of the less frequent incidence of side-effects.[47] Studies show mixed results with regard to benefit, but none show harm.[4]

Multiple studies have described the use of small-dose ketamine as adjuvant to opioid analgesics. There is a statistically significant decrease in pain intensity at 6, 12, 24 and 48hours post-operatively with the use of ketamine. Morphine consumption is significantly decreased but opioid related side-effects are not affected. There is a high risk of hallucinations in sedated patients but this risk is low when undergoing GA.[48] The opioid-sparing effect of a single dose ketamine of 0.1-0.15mg/kg has also been demonstrated after painful orthopedic and intra-abdominal surgeries with no increase in side-effects.[49,50] The addition of ketamine to morphine PCA in a 1:1 ratio with a lockout interval of 8min has also been described with positive effects after major orthopedic procedures.[51] However after major abdominal surgery no significant benefit could be found and it was associated with increased side-effects including vivid dreams.[52]

Ketamine is also useful during monitored anaesthesia. The addition of ketamine 4-18ug/kg/min to propofol 30-90ug/kg/min diminished the incidence of respiratory depression while demonstrating positive mood effects postoperatively. It was also suggested that it may even provide for an earlier recovery of cognitive function.[53,54]

The preemptive analgesic effects have been under investigation due to its ability to block central NMDA receptors, but well controlled clinical studies have not been able to verify this effect.[55,56] Pre-emptive administration has shown decreased postoperative opioid requirements in some studies[50] and in others have demonstrated no difference on opioid sparing effect when comparing dose given pre-incision or at end of surgery.[49]

Limited data is available for opioid-tolerant patients. Reduction in immediate postoperative opioid requirements with pain scores reduced by 25% was reported by one RCT. Opioid use at 6weeks after surgery was reduced by 71%.[4] In the presence of opioid-resistant pain, a modest dose of ketamine 0.25mg/kg post-operatively was shown to improve analgesia.[57] Hyperalgesia caused by acute tolerance to opioid analgesia may be prevented by repeated doses of ketamine.[17] Pretreatment with ketamine has shown attenuation or ablation of opioid-induced hyperalgesia. Ketamine seems to hold particular benefit for the opioid-tolerant patient and significantly improves the postoperative management during the first few days following surgery.[4]

Ketamine dose has not been clearly defined but doses exceeding 0.5mg/kg as a bolus or infusions exceeding 0.5mg/kg/hr have been found to be associated with increased neuropsychiatric effects.[29] At doses less than 0.5mg/kg it reduces postoperative analgesic needs and this is especially seen in the opioid tolerant patient.[29] Some authors advocate that ketamine should be used in all surgical cases, with increased doses and infusions for patients with high opioid tolerance. Opioid-tolerant patients should receive a 5-10mg/hr ketamine infusion postoperatively and this may be continued for weeks.[4]

Side-effects of ketamine include hypertension, arrhythmias, nausea and vomiting, diplopia and nystagmus, psychomimetic reactions and dizziness and confusion.[10]

Dexamethasone

Dexamethasone is a potent corticosteroid devoid of mineralocorticoid effects.[4]

Dexamethasone is recognized as an effective antiemetic when given at a dose of 50mcg/kg at induction. A higher dose of 100mcg/kg has been found to additionally reduce analgesic requirements postoperatively.[58] Reduced pain scores as well as decreased PONV have been demonstrated for more than 24hours postoperatively. This may be explained by its anti-inflammatory effects on the wound with less edema leading to less pain.[3] Dexamethasone demonstrates opioid sparing effects at intermediate doses of 0.11-0.2mg/kg and reduces early and late pain at rest and with movement. Low dose dexamethasone does not demonstrate opioid-sparing effects.[58]

It is suggested that dexamethasone be given prior to incision as this may be important in limiting inflammation.[3,59] Pre-operative administration seems to be more beneficial as the onset of action is 1 - 2 hours, but this is associated with a painful perineal sensation.[58,59] The optimal dose is suggested as 0.1 to 0.2mg/kg.[59]

Gabapentinoids

Gabapentinoids limit facilitation of pain transmission by inhibiting the voltage gated calcium channels on sensory neurons.[29] Gabapentin is a structural analog of gamma-aminobutyric acid. It is an anticonvulsant that has proven benefit in the management of neuropathic pain. Multiple studies suggest a possible role for acute postoperative pain.[60-62] It is used in doses of 600-800mg. Pregabalin is used in doses of 150 – 300mg given twice daily starting the night before surgery. The most troublesome side-effect is dizziness but it can still be useful where the type of surgery will delay mobilization e.g. spinal surgery.[29]

Gabapentin reduces opioid consumption by about 33% but drowsiness and loss of coordination can last for 12-24hrs postoperatively.[4] Postoperative analgesic requirement can be significantly reduced with gabapentin (1.2g po) given as a premedication. This does not increase side-effects.[60] Continuation of gabapentin postoperatively, reduces postoperative opioid use as well as pain related to movement after breast surgery. However this does not affect the overall incidence of chronic pain.[61] Pregabalin is reported to possess analgesic effect comparable to that of ibuprofen in acute dental pain.[62] Preoperative administration of 600mg of pregabalin significantly decreases postoperative pain as well as opioid use but at the cost of increased incidence of dizziness.[63]

CAN OPIOID MINIMIZATION IMPROVE OUTCOMES AFTER MAJOR SURGERY?

1. <u>Fast tracking/ERAS</u>
   Evidence has shown beneficial effects related to ERAS protocols. A decreased duration of hospital stay translates to reduced healthcare costs and perhaps more importantly, increases patient satisfaction.[16] Early mobilization and resumption of enteral nutrition are key aims of ERAS. In order to facilitate postoperative rehabilitation and mobilization, good pain control is essential. This can result in earlier resumption of normal activities. Opioid minimization is one of the components of a successful ERAS strategy as opioids can be associated with side-effects which prevent a smooth recovery.[29] While opioids are currently the mainstay of severe

postoperative pain relief, their use prolongs hospital length of stay. This is directly related to opioid induced adverse effects which includes excessive sedation, respiratory depression, high incidence of PONV, urinary retention and ileus.[11] Greater opioid use before surgery is associated with slower recovery time, longer hospital stay and worse outcomes after surgery.[64]

Fast-track guidelines with multimodal analgesia aim to reduce postoperative pain, minimize these opioid-related side effects and improve early recovery to decrease length of hospital stay.[16] Multimodal analgesia is therefor advocated[9] as well as strong reduction of opioids postoperatively to improve healing and to avoid immunological suppression.[3]

Perioperative infusions of lignocaine has been associated with better postoperative pain control at rest, during cough and during movement at 6hours. It reduces opioid requirement with a reduction in opioid related side-effects. Faster recovery from ileus and bowel recovery occurring about 1 day faster demonstrates a significant benefit after abdominal surgery. Total length of hospital stay is decreased by 1 day. Nausea and vomiting is also reported to be reduced.[31]

Esmolol has been found to enhance fast-track protocols and reduces time to home-readiness of patients undergoing outpatient surgery.[5] Perioperative esmolol has been shown to reduce anaesthetic requirements, decrease perioperative opioid use, decrease incidence of postoperative N+V, lead to an earlier discharge and increase patient satisfaction.[1]

2. Day case/outpatient setting

Complex operations are increasingly being performed as day case surgery.[10] Effective postoperative analgesia is one of the major challenges of outpatient surgery. The aim is to allow earlier and safe discharge. Opioids are widely used in the ambulatory setting but multiple adverse effects often lead to delayed discharge.[5] Given the need to facilitate an earlier hospital discharge, improving postoperative pain is an increasingly important issue for all anaesthetists.[10] A multimodal approach would provide opioid-sparing, good quality pain relief thus facilitating earlier discharge.[5]

3. OSA/obesity

Recent ASA guidelines recommend avoidance of perioperative respiratory depressants in patients with obstructive sleep apnoea.[3] Sleep-disordered breathing such as obstructive sleep apnea syndrome associated with opioids are reported to occur frequently and the severity is increased by the use of opioids.

Respiratory depression is a large problem especially during the first night after an opioid anaesthetic. The use of a multimodal analgesia regime reduces the occurrence of postoperative OSAS. It was initially thought that short acting opioids like remifentanil is ideal as the effect is immediately worn off post-operatively, but increased postoperative pain caused by central sensitization actually requires additional opioid treatment postoperatively.[19] Magnesium as part of a multimodal regimen for obese patients undergoing gastric bypass surgery was shown to produce postoperative analgesia similar to fentanyl, with fewer side-effects.[44]

4. Oncology/Cancer recurrence

The effect of opioids on the rate of cancer metastases has mainly been studied in animal models. It does appear that opioids may indeed have a tumor enhancing effect in vitro. It is multifactorial and includes an increase in the mu-receptors, angiogenesis and tumor bulk. Definitive evidence of effect in humans is still lacking.[65]

Opioids have been shown to cause immunosuppression and stimulate malignant cells in vitro, though adjunct analgesics may additionally promote tumor cell growth. This has led many to hypothesize that regional analgesic techniques may offer survival advantage to systemic analgesics. Thus far, the data do not support specific analgesic recommendations for the cancer patient and ongoing trials are under way.[66] Better survival has been demonstrated when no opioids are used intraoperatively[3] and local anaesthetics are associated with better cure rates and reduced recurrence after cancer surgery.[67]

5. POCD in the elderly

Postoperative cognitive dysfunction is a frequent problem in elderly patients following narcotic anaesthesia. The occurrence of postoperative cognitive dysfunction seems to be lower with more natural sleep experienced from the first postoperative day when opioids are avoided.[3]

6. Chronic pain syndromes/complex regional pain syndromes[3]

Multimodal analgesia also aims to reduce the risk of chronic postoperative pain. Research on the influence of commonly used analgesics on the development of chronic pain is limited.[22] The use of ketamine in opioid-dependent patients with chronic back pain demonstrated reduced morphine consumption up to 48hours following back surgery. At 6 weeks follow up the average reported pain intensity was also significantly reduced.[7]

7. Improved quality of recovery and patient satisfaction

The Joint Commission on Accreditation of Healthcare Organizations have suggested that excessive postoperative use of opioids can decrease patient satisfaction.[10] Opioid minimization has been shown to reduce nausea, vomiting, constipation, urinary retention, respiratory depression and sedation and can improve quality of recovery for postoperative patients. [10]

PROBLEMS WITH OPIOID FREE ANAESTHESIA[10]

- The sympathetic block achieved with alpha-2 agonists is not as fast and easily titratable as with opioids.

- There are also side-effects associated with the different adjuvant drugs:
  - Local anaesthetics
    - Residual motor weakness
    - Peripheral nerve irritation
    - Allergic reactions
    - Sympathomimetic effects
    - Cardiac arrhythmias and toxicity

  - Paracetamol
    - GI upset
    - Hepatotoxicity
    - Sweating
    - Agranulocytosis

  - NSAIDs
    - Bleeding
    - GI bleeding
    - Renal tubular dysfunction
    - Allergic reactions
    - Pedal edema
    - Bronchospasm
    - Hypertension

  - NMDA antagonists
    - Hypertension
    - Diplopia and nystagmus
    - Nausea and vomiting
    - Dizziness and confusion
    - Psychomimetic reaction
    - Cardiac arrhythmias
    - Muscle weakness and sedation

  - Alpha-2 agonists
    - Bradycardia and hypotension
    - Sedation
    - Dizziness

  - Beta-blockers
    - Hypotension and bradycardia
    - Heart block
    - Bronchospasm
    - Heart failure

  - Gabapentin
    - Somnolence and dizziness
    - Peripheral edema[10]

Indications for OFA

- Obese patients with obstructive sleep apnoea
- Pulmonary disease e.g. asthma, COPD
- Acute and chronic opioid addiction
- Previous hyperalgesia problems
- Complex regional pain syndromes
- Chronic fatigue and immune dysfunction syndrome?
- Oncological surgery?
- Inflammatory diseases?[3]

Absolute contra-indications to OFA

- Allergy to any of the adjuvant drugs

Relative contra-indications to OFA

- Disorders of autonomic failure e.g. orthostatic hypotension
  - It has been suggested that using a smaller dose of dexmedetomidine could lessen the effect.
- CVS disease
  - Known critical coronary stenosis or acute coronary ischemia
  - Consider adding nicardipine (coronary vasodilation) and slower loading of dexmedetomidine (less hypertension and vasoconstriction).
  - Heart block, extreme bradycardia
- Non-stabilised hypovolemic shock and polytrauma patients
  - Peripheral vasodilation can limit the perfusion of critical central organs while opioids induce vasoconstriction.
- Controlled hypotension for minimal blood loss
  - This requires cardiac output depression which is easier achieved with high dose remifentanil. If an opioid free technique is used, additional drugs will be required to reduce the cardiac output e.g. beta-blockers.
- Elderly patients on beta-blockers
  - Consider using lower dose of dexmedetomidine.[3]

PRACTICES IN OTHER COUNTRIES

Opioid free anaesthesia has already been a reality in many parts of the world and some units practice it routinely. The following is a suggested postoperative infusion suggested at a recent presentation from the ASA meeting in New Orleans:

Ketamine 100mg Dexmedetomidine 100mcg Lignocaine 100mg Magnesium sulphate 5g Added to 1l saline PCA pump or elastometric infusion pump @ 12ml/hr No patient or clinician controlled boluses allowed[29]

In Bruges the use of opioid free anaesthesia and analgesia have increased patient satisfaction with less pain postoperatively, better sleep the first night and decreased opioid related side effects experienced by patients. Their postoperative ward nurses recognize immediately which patients received OFA.

Opioid free anaesthesia was introduced in their unit in 2011 and started with very low dose ketamine, clonidine and beta-blockers together with local wound infiltration. In 2012, dexmedetomidine became available in Europe and they started running infusions intraoperatively, replacing clonidine at induction. The full dose of 1 to 1.2ug/kg/hr can be given but it should be remembered that rapid awakening is not possible for a procedure of a few hours making this method not practical either.

Lignocaine and magnesium was given at induction and infusion continued intraoperatively. They found that when paracetamol and ketorolac or diclofenac was also added, perfect postoperative pain management was possible without opioids or epidurals even in large laparotomies.

0.6 – 1MAC of inhalation was added to the regime to achieve hypnosis without awareness. Propofol was substituted by inhalational agents as they found the dose of propofol to achieve sufficient hypnosis without opioids to be too high. Using propofol combined with sympathetic block is possible but requires very high doses while inhalation can be given below 1 MAC. They emphasize that correct hypnotics given remain important and BIS or entropy can measure this. Clinical factors like HR and BP and more specific tools like SSI, HR variability or Qnox can measure the sympathetic block. NMT should measure NMB.

The respiratory centre is not depressed when opioids are avoided but patients are often easily ventilated on pressure support ventilation. Today several versions of the OFA approach in Bruges exist and the following is just one of their methods:[3]

Pre-operatively an infusion of lignocaine 0,1% plus 50mg ketamine and 5g magnesium sulphate (added to 1l) is started and continued perioperatively at 1ml/kg/hr. This equates to lignocaine at 1mg/kg/hr, magnesium at 5mg/kg/hr and ketamine at 50ug/kg/hr.

Prior to induction dexamethasone 10mg is given and droperidol 1,25mg (given as PONV prophylaxis).

At induction, dexmedetomidine loading is achieved with 0,5 to 1ug/kg over 15minutes. The dose can be decreased in surgery of less than 1hour duration, elderly or weak sympathetic system. Lignocaine 1% 1mg/kg, propofol induction dose of 2.5mg/kg and rocuronium if needed is given. Magnesium sulphate 40mg/kg is given after induction.

For maintenance, volatiles are used at 0.7 to 1 MAC and BIS maintained between 40-60%. Propofol could also be used at 10mg/kg/hr. If the surgery lasts longer than 2hours then an infusion of dexmedetomidine at 0.5ug/kg/hr can be run and should be stopped 30min prior to the end of surgery. Continue the infusion with lignocaine, magnesium and ketamine. Metoprolate and nicardipine are kept available if a rapid decrease in heart rate or BP is needed. A second dose of dexmedetomidine could be used but its effect is delayed.

Analgesics should be loaded up before the end of surgery with paracetamol and diclofenac.
Postoperatively continue with paracetamol 1g 6hourly and diclofenac 75mg every 12hours. Continue the sympathetic block with clonidine 75 to 150ug. Continue with low dose of the ketamine, magnesium sulphate and lignocaine infusion at 1ml/kg/hr. If the patient complains of pain after 30min, a low dose of morphine 3-5mg can be given in the recovery room.[3]

SO WHAT IS THE CLINICAL USE OF OPIOIDS TODAY?

Opioids are increasingly becoming rescue analgesics only. This places recovery room nurses in the pivotal role of deciding when initiation of opioid therapy is warranted. For minor procedures e.g. breast biopsy, arthroscopic knee surgery for which opioids is possibly unnecessary, it is suggested to use non-opioid adjuvants and to counsel the patient on the risks and side effects of opioids. This creates a motivation with the patient to remain opioid free. For major procedures e.g. exploratory laparotomy, long-acting opiates e.g. hydromorphone or morphine can be administered at emergence only.[4]

CONCLUSION

Opioid free anaesthesia seems to be the new buzz phrase in anaesthesia but there is still a cloud of uncertainty hanging over it.

The goals of optimal peri-operative analgesia is to reduce pain scores and enable earlier mobilization with enhanced rehabilitation, faster discharge and improved patient satisfaction. By reducing opioid related adverse effects, opioid free anaesthesia aims to enhance these goals.

The use of new therapeutic modalities should be considered on an individual basis and the risk-benefit ratio should be borne in mind. More research is needed to fully elucidate the role of opioid free anaesthesia in every day anaesthetic practice as well as the important role it may have in the prevention of chronic pain.[10]

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