

## The Benefits of Opioid Free Anesthesia and the Precautions Necessary When Employing It

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### Abstract

The use of opioids in the perioperative period is associated with respiratory depression, impaired gastrointestinal function, post-operative nausea and vomiting (PONV), pruritus, urinary retention, delirium and the potential for developing opioid addiction. Currently the United States is experiencing an epidemic of prescription opioid abuse and deaths from overdose. Many addicts develop their addiction during a routine surgical admission to hospital. More people now die from overdose of synthetic prescription opioids than from heroin and other street drugs. Public education campaigns teaching family members of addicts to reverse opioid induced respiratory depression with naloxone are currently underway. Preventing the development of addiction in the first place during and after the surgical admission however will be more successful at saving lives. Primary prevention of opioid addiction is possible when non-opioid analgesic drugs are used. Employing alternative analgesic drugs in the peri-operative period that have a lower addiction potential and less respiratory depression has therefore become a matter of great national importance. Many powerful non-opioid analgesics are currently available that have more favorable side effect profiles and a lower potential for developing addiction. However, these medications are currently not used as often in routine clinical practice as they should be. Replacing opioids with other analgesics will not only reduce the development of opioid addiction but will also lead to better perioperative outcomes and enhanced patient recovery. This article briefly reviews the opioid alternatives that can significantly reduce or even entirely eliminate the perioperative use of opioids in the majority of surgical procedures.

### Keywords

Opioids, Analgesia, Perioperative

### Introduction

Opioid analgesic drugs have been the most commonly used perioperative pain-relieving medications for a very long time. While they are effective at relieving somatic pain they, unfortunately, do not eliminate neuropathic pain and have a profound potential for developing addiction [1,2]. Opioid addiction is currently an epidemic in the United States and overdose deaths from synthetic opioid drugs have been skyrocketing over the last decade. (Figure 1)

Many addicts trace the origin of their opioid addiction back to when they were admitted to the hospital and received opioids as an analgesic modality. There is therefore a large iatrogenic component to the current opioid abuse epidemic. High potency opioids like hydrocodone and oxycodone have a street value that far exceeds that of heroin. [1] Prescription opioids now have become a common cause of overdose deaths. A national strategy needs to be developed to reverse the current epidemic of addiction and overdose deaths. There are currently different approaches to trying to reduce these overdose deaths. Educating addicts, their friends and families about how and when to administer naloxone can be an effective method of secondary prevention [3]. Primary prevention to stop an opioid addiction from developing during the perioperative period in the first place should however be the ultimate goal. In this article we explore the use of non-opioid analgesic drugs to both reduce the risk of developing opioid addiction and the occurrence of opioid related side effects. The use of these alternative drugs in combination as part of a multimodal strategy can lead to enhanced recovery after surgery with a lower potential for developing addiction. Substituting the administration of opioids with alternative analgesics in the perioperative period should be of great priority for health care providers. There should be a frank discussion with patients about the risk of developing an opioid addiction before the operation and counselling should be conducted when the patient's opioid use appears to be excessive after the operation. Prescription opioid refills will need to be limited and carefully reviewed [4].

### Opioid Related Side Effects

The most significant opioid side effect is respiratory depression. This is especially important in patients with obesity, sleep apnea, chronic obstructive pulmonary disease and operations that are associated with a high incidence of post-op respiratory failure [5]. Impaired gastro-intestinal function is a major issue in bowel surgery because postoperative ileus may

## Drugs Involved in U.S. Overdose Deaths, 2000 to 2016

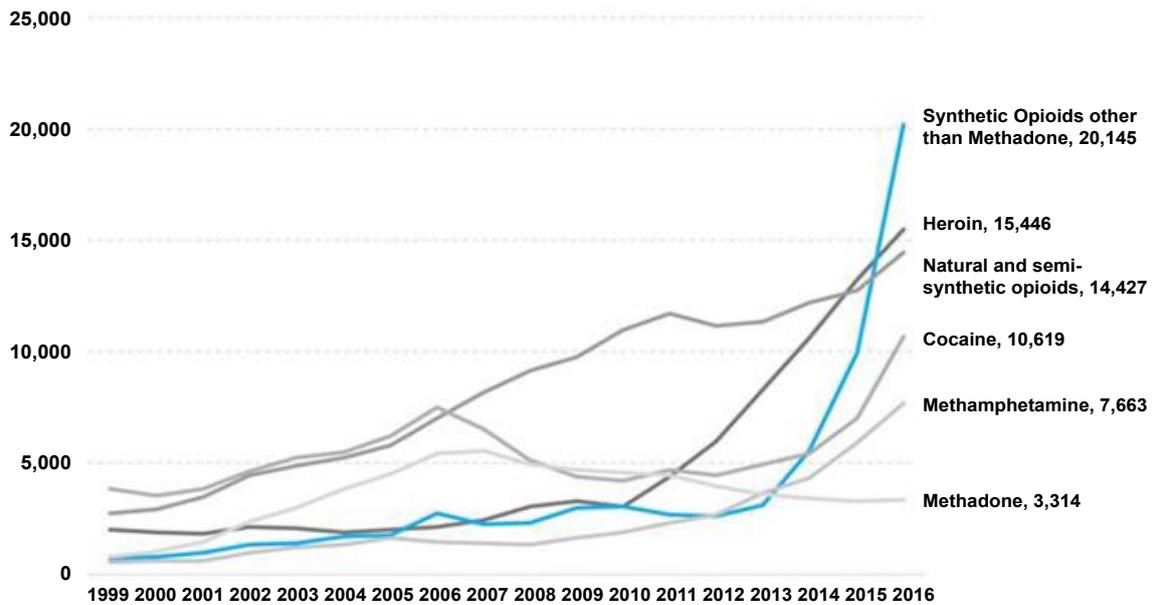


Figure 1: Drugs involved in U.S. Overdose deaths, 2000 to 2016.

lead to an anastomotic leak. When opioids are used liberally in major operations opioid induced bowel distension pushes the diaphragm in a cephalad direction and causes atelectasis in both lung bases. This abdominal distension increases the work of breathing and leads to hypoxemia because the collapsed lung bases no longer take part in gas exchange. This often causes postoperative respiratory failure with re-intubation. Abdominal distension is also a common cause for surgical wound dehiscence. Opioid induced gastro-paresis is also a significant contributor to aspiration during anesthesia induction. In the critical care unit (CCU) it leads to inability to absorb nasogastric feeds and malnutrition. The use of opioids as standard critical care sedatives should therefore be eliminated as better agents like dexmedetomidine have become available [6]. Opioid induced PONV is a particularly significant problem following eye surgery, upper gastrointestinal surgery and head and neck and neurosurgery where the Valsalva maneuver associated with the vomiting process may precipitate bleeding or a cerebrospinal fluid leak. Pruritus can be a more significant problem in the recovery room than pain. This is often treated with antihistamines that are only partially effective at alleviating the itch and cause a lot of unwanted sedation. Urinary retention leads to catheterization and urinary tract infections. Postoperative delirium is commonly induced by opioids and can be treated by employing alternative pain management strategies. Opioids depress cell mediated immunity and in some studies have been found to be associated with an increased tumor recurrence rate after cancer surgery [7,8]. Until further evidence

becomes available opioids should be used with caution in cancer surgery.

## Alternatives to Opioids in Perioperative Care

### Dexmedetomidine

Dexmedetomidine is an alpha-2 agonist with analgesic action that causes far less hypotension than clonidine. Blood pressure transiently rises following dexmedetomidine administration followed by a drop to ten percent below baseline values [9]. Unlike opioids it is not associated with significant respiratory depression, PONV, pruritus, constipation, ileus or delirium [10]. It can reduce intraoperative opioid administration by more than 50% [11]. In laparoscopic surgeries, it has been found to provide adequate analgesia when used as the only analgesic [12]. It has been shown to provide better heart rate control post intubation than fentanyl when used for intravenous induction [13]. It has been used as a PCA drug in combination with opioids and has been found to provide better analgesia with less PONV than opioids alone [14,15]. It should be used in patients with sleep apnea, obesity, gastric bypass surgery and a history of PONV or delirium. It is a powerful bronchodilator and should be used in patients with chronic obstructive airway disease and asthma [16]. It is also an anxiolytic and 20 mcg dexmedetomidine can replace 2 mg midazolam as a pre-operative anxiolytic. It provides enhanced recovery and patient satisfaction after laparotomy [17] and should be considered as part of any enhanced recovery after surgery (ERAS) program. It has a much lower addictive potential than opioids and should therefore be used in preference to opioids as a first line

**Table 1:** Intravenous and Oral Opioid Replacement Drugs.

| Drug               | Dosage                                       |
|--------------------|--|
| IV Dexmedetomidine | 0.25 mcg/kg boluses (0.5-mcg/kg/hr infusion) |
| IV Acetaminophen   | 15 mg/kg every 6 hours                       |
| IV Ketorolac       | 30 mg every 6 hours                          |
| IV Ketamine        | 0.25 mg/kg boluses (0.1 mg/kg/hr infusion)   |
| IV Lidocaine       | 1 mg/kg loading dose (1-2 mg/kg/hr infusion) |
| Oral Gabapentin    | 300 mg PO daily                              |
| Oral Pregabalin    | 150 mg PO daily                              |
| IV Magnesium       | 30 mg/kg loading dose (10 mg/kg/hr infusion) |

analgesic drug. It has long half-life of two hours and it can be safely administered by intravenous (IV) bolus doses until the desired effect is achieved. Bradycardia is the major dose limiting side effect and this responds readily to atropine [9].

### Intravenous acetaminophen

Acetaminophen is a non-opioid analgesic drug with potent antipyretic but very weak anti-inflammatory action [18]. The IV formulation has a more potent analgesic action with faster onset and much higher plasma levels than the oral formulation [19]. There is also less liver toxicity with the IV formulation because IV administration bypasses the first pass metabolism in the liver. There was a 46% reduction in opioid use on day 1 with this drug following hip and knee surgeries with less PONV. Acetaminophen can be toxic to the liver when administered in overdose and the daily IV administration should not exceed 15 mg/kg every 6 hours. The combined daily maximum should not exceed 4 g [20]. Care needs to be taken when using this drug in patients with liver disease and the maximal daily dose in these patients should be limited to 2 g/day [21] (Table 1).

### Intravenous Ketorolac

Ketorolac is a non-steroidal anti-inflammatory drug with significant analgesic action [22]. It can be used to limit opioid side effects and is particularly useful in treating painful uterine cramps which are prostaglandin mediated. It should be avoided in asthmatics because interference with the prostaglandin mechanism can precipitate bronchospasm. There is also the risk of bleeding, renal impairment and gastritis and peptic ulceration when administered over several days. Bleeding was not an issue after breast surgery [23] but after circumcision the ketorolac group had more bleeding [24]. Unlike ketorolac the selective cyclooxygenase 2 inhibitors are not associated with bleeding but have a higher rate of thrombotic events and should be avoided in patients at risk

for myocardial infarction or stroke. The opioid sparing effect of ketorolac has been associated with a reduced cancer recurrence rate after breast cancer surgery [25]. Ketorolac also interferes with bone fusion after back surgery and should not be used in these cases [26]. Ketorolac should also best be avoided in the elderly with pre-existing renal impairment.

### Ketamine

Ketamine is an NMDA receptor antagonist that has profound analgesic effects at sub-anesthetic doses. Bolus doses should be limited to 0.25 mg/kg to prevent tachycardia and hypertension. Because of its long half-life (2-3 hours) it is reasonable to administer it via IV bolus doses rather than continuing infusion. Bolus doses larger than 0.25 mg/kg should however be avoided especially in patients with coronary artery disease because the resulting tachycardia and hypertension may lead to myocardial ischemia. Ketamine is associated with the wind-down phenomenon [27] and results in reduced pain during the post-operative period. It is also effective at treating neuropathic pain that usually does not respond to treatment with opioids. Recently it has also been noted to have a profound antidepressant effect [28,29]. The most significant side effect is a dysphoric syndrome with hallucinations and out of body experiences at higher doses. This can be suppressed with benzodiazepines but is best avoided by not administering doses greater than 0.5 mg/kg [30,31]. The addictive potential of this drug is, unfortunately, very high and while it can reduce the side effects of opioids it may not be a solution to the current prescription drug abuse epidemic.

### Intravenous lidocaine

Lidocaine is an amino-amide local anesthetic that has a profound analgesic effect and has been shown to significantly reduce opioid requirements and side effects. The loading dose is 1-2 mg/kg followed by an infusion of 1-2 mg/kg/hr. [32] The rate should be reduced by 50% every 6 hours. In abdominal operations it reduced ileus, PONV [33] and has been shown to be of similar efficacy to epidural administration of local anesthetic. It may be an effective neuroprotective agent to prevent early post-operative cognitive dysfunction [34]. It is also effective for neuropathic pain. Lidocaine is metabolized in the liver and the administration rate needs to be reduced in low cardiac output states that are associated with poor liver perfusion in order to prevent toxicity. Side effects are perioral paresthesia, metallic taste, tinnitus and seizures [35]. Under anesthesia the only manifestations of toxicity may be bradycardia and wide QRS complexes. Lidocaine toxicity is more likely to manifest when the plasma level reaches 5 mcg/ml [36]. A bolus dose of 1 mg/kg followed by an infusion of 1.5 mg/kg/hr usual-

ly leads to a plasma concentration of about 2 mcg/ml [37]. So there is an inbuilt margin of safety when administering this dose. Cardiac arrest is possible with extreme toxicity and given its low therapeutic index it is wise to administer lidocaine by continuous infusion rather than by large intravenous bolus doses. If local anesthetic systemic toxicity is suspected a bolus dose of 1.5 ml/kg intralipid followed by an infusion of 0.25 ml/kg/min should be administered [35].

### Gabapentin/Pregabalin

Gabapentinoids are derivatives of the inhibitory neurotransmitter gamma aminobutyric acid (GABA). Both gabapentin 300 mg PO and pregabalin 150 mg PO are effective analgesics that are also useful in neuropathic pain. Their use leads to lower pain scores, reduced opioid consumption and opioid related side effects [38,39]. They can be continued into the post-operative period. Excessive sedation, dizziness and visual disturbances can be a problem with high doses after prolonged periods.

### Magnesium

Magnesium (Mg) has analgesic action by regulating calcium flux into the cell and acting as an NMDA receptor antagonist. It also suppresses neuropathic pain. It has been shown to reduce the need for post-operative opioids and improve post-operative pain scores [40]. The loading dose is 30-50 mg/kg and it may be followed up by an intravenous infusion of 10 mg/kg/hr.

Side effects are hypotension and bradycardia that respond readily to standard therapy but are more common when higher doses are administered. When using Mg intra-operatively it is important to reduce the amount of muscle relaxants and anesthetic drugs that are administered to prevent residual neuromus-

cular block and delayed emergence from anesthesia. Mg potentiates neuromuscular blocking drugs and CNS depressants and these effects need to be taken into consideration. The depth of neuromuscular block should be carefully monitored and adequacy of neuromuscular reversal should be confirmed prior to extubation.

### Regional blocks and centroneuraxial blocks

Many procedures can be performed under regional or centroneuraxial anesthesia. The use of catheters for ongoing post-operative infusion can greatly limit or entirely eliminate the use of perioperative opioids. Many perineural regional techniques like paravertebral and pectoral nerve blocks have been used successfully [41]. Local wound infiltration with local anesthetic has become common in lower limb joint replacement surgery because of great efficacy and the absence of motor block [42]. Transversus abdominis plane (TAP) blocks and the erector spinae plane (ESP) block for abdominal and thoracic surgeries lead to better analgesia and reduced opioid use [43,44].

### Mixed agonist/antagonist drugs acting on opioid receptors

Mixed agonist/antagonist drugs acting on opioid receptors like dezocine and buprenorphine are generally regarded as less addictive and respiratory depressant than the full agonists but they may also have a lower analgesic ceiling than the full agonists. These drugs do, however, offer significant advantages in the treatment of opioid addicted patients. Dezocine has been shown to alleviate morphine-induced dependence and improve patient experience in both preclinical and clinical studies [45,46].

In summary, the perioperative use of opioids has

**Table 2:** Risk and benefits of opioid and non-opioid analgesics.

|          | Opioid Analgesia  | Opioid free/ Opioid Sparing Analgesia  |
|----------|---|--|
| Risks    | Respiratory depression<br>Need for post-op ventilation with ventilator associated pneumonia<br>Addiction<br>Nausea & Vomiting<br>Gastrointestinal dysfunction, ileus<br>Pruritus<br>Urinary retention | Bradycardia with dexmedetomidine<br>Hepatic damage with acetaminophen<br>Bleeding, renal impairment and bronchospasm with ketorolac<br>Hallucinations, tachycardia and addiction with ketamine<br>Tinnitus, seizures and cardiac arrest with lidocaine<br>Sedation with gabapentin<br>Hypotension with magnesium |
| Benefits | Analgesia<br>Ready acceptance of poor patient outcomes by peers, due to the conventional nature of the analgesic therapy  | No respiratory depression<br>No addiction except for ketamine<br>Less need for post op ventilation<br>No nausea and vomiting<br>No gastrointestinal dysfunction and ileus<br>No pruritus<br>No urinary retention   |

many detrimental effects on health care outcomes and is currently precipitating an epidemic of prescription opioid addiction and overdose deaths throughout the United States. Many alternative non-opioid analgesic drugs with a lower addiction potential and a better side effect profile are available but are currently underused. At present there is a campaign to educate addicts and their families and friends about naloxone to curb opioid overdose deaths. To get the current prescription opioid abuse epidemic under control however primary prevention by limiting the administration of opioids during hospitalizations will be necessary. Opioid free anesthesia can be achieved during most operations by employing alternative analgesics. The use of these non-opioid analgesic drugs as the alternatives to opioids should be continued after discharge from hospital. Opioid prescriptions and refills will need to be limited and ongoing opioid requests by the patient will need to be assessed carefully. Anesthesia care providers and surgeons need to understand that their perioperative pain management has lasting effects that have the potential to negatively affect their patients for the rest of their lives (Table 2).

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