

# An Evidence-Based Opioid-Free Anesthetic Technique to Manage Perioperative and Periprocedural Pain

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**Background:** The epidemic of opioid abuse is increasing, and the number of deaths secondary to opioid overdose is also increasing. Recent attention has focused on opioid prescribing and management of chronic pain. However, opioid use in perioperative and periprocedural patients, whether they have chronic pain or exhibit new persistent opioid abuse after a procedure, has received little attention.

**Methods:** We present an evidence-based technique that combines subanesthetic infusions of lidocaine and dexmedetomidine supplemented with other intravenous agents and a low dose of inhaled anesthetic.

**Results:** Based on evidence of drug action and interaction, an opioid-free anesthetic can be delivered successfully. We present the cases of 2 patients in whom the opioid-free anesthetic technique was used with a successful outcome, adequate pain management, and avoidance of opioid drugs.

**Conclusion:** This anesthetic prescription can be useful for opioid-naïve patients as well as for patients with chronic pain that is managed with opioids.

**Keywords:** Anesthesia, balanced anesthesia, dexmedetomidine, lidocaine, opioid-related disorders, perioperative care

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## INTRODUCTION

Deaths from opioid overdose continue to rise in the United States. The number of prescriptions for opioids quadrupled between 1999 and 2015, and access to illegal synthetic opioids such as fentanyl has also.<sup>1</sup> The problem has become so severe on US college campuses that some schools have begun stocking naloxone to reverse opioid-induced respiratory depression in emergency situations.<sup>2</sup> A study published in 2008 of 12,739 surgical inpatients noted a correlation between persistent perioperative opioid use following surgical procedures and mortality.<sup>3</sup> In 2017, Brummett et al reported data on 36,177 surgical patients in whom new persistent opioid use—defined as an opioid prescription fulfillment 90-180 days after the surgical procedure—was identified after both major and minor surgical procedures, and the rate of new persistent opioid abuse of approximately 6% was similar between the 2 groups.<sup>4</sup>

In 2016, the Centers for Disease Control and Prevention released guidelines for prescribing opioids to treat chronic pain.<sup>5</sup> However, focus on opioid prescribing for perioperative pain has been lacking, leading Birkmeyer to conclude, “Given the declining rates of morbidity and mortality following common elective procedures, new persistent opioid use represents an important, common, and unrecognized complication of perioperative care.”<sup>6</sup>

We present an evidence-based opioid-free anesthetic technique employing subanesthetic doses of intravenous anesthetic agents that are already in use but not specifically used in this combination. In addition, we present 2 cases that illustrate the use of this anesthetic regimen.

## INTRAVENOUS ANESTHETIC AGENTS

The introduction of intravenous anesthetic agents is of historic interest. John Lundy of Mayo Clinic published an initial report in *Minnesota Medicine* in 1926;<sup>7</sup> a full report followed in the *Journal of the American Medical Association* in 1931.<sup>8</sup> At that time, intravenous access was not standard practice. Lundy introduced the term *balanced anesthesia* and suggested that using lower doses of more than one anesthetic agent improved outcomes. This thought process led to the adoption of the so-called *nitrous oxide narcotic anesthetic*: nitrous oxide combined with oxygen in a 60%:40% ratio supplemented with intermittent intravenous dosing of morphine sulfate.

In 1993, Kehlet and Dahl introduced the term *multimodal analgesia* for management of postoperative pain, along with the term *balanced analgesia*,<sup>9</sup> and Woolf and Chong introduced the term *preemptive analgesia*.<sup>10</sup> Thus, the confluence of volatile anesthetic agents, intravenous anesthetic agents, and regional and neuraxial anesthetic techniques

gained favor among clinicians for improved pain management. Who first proposed continuous infusion of lidocaine for anesthesia and analgesia is not clear, but both surgical and medical literature report the use of the technique resulting in a more rapid return of bowel function, improved postoperative analgesia, and shorter length of stay for surgical patients compared to a control group of surgical patients.<sup>11,12</sup> Continuous infusion of anesthetic and analgesic agents became more popular as drugs with a shorter half-life ( $t_{1/2\beta}$ ) than other intravenous anesthetic agents and a predictable volume of distribution ( $V_D$ ) were developed.<sup>13</sup>

## OPIOID-FREE ANESTHETIC AGENTS

The anesthetic technique we propose is based on a multimodal approach using specific agents that have anesthetic or analgesic properties, administered in subanesthetic doses to achieve the desired effect. Continuous infusions of lidocaine and dexmedetomidine are supplemented with a low dose of a volatile anesthetic agent and intermittent dosing of acetaminophen, ketamine, ibuprofen, and ketorolac.

### Lidocaine

Lidocaine has analgesic,<sup>14-16</sup> antiinflammatory,<sup>16-18</sup> and antihyperalgesic properties.<sup>19,20</sup> Because lidocaine infusion has been used to treat cardiac arrhythmias, its plasma levels for therapeutic effect and specific organ toxicity are well established (Table). Lidocaine has 2 active metabolites: monoethylglycinexylidide (MEGX) that is further metabolized to xylidine. MEGX is 80% as active as lidocaine, and xylidine is 10% as active as lidocaine (Figure).<sup>14</sup> The  $t_{1/2\beta}$  of MEGX is 2.5-3.0 hours, whereas the  $t_{1/2\beta}$  of lidocaine is 1.5-2.0 hours.<sup>14</sup> Lidocaine is metabolized in the liver and excreted by the kidneys.<sup>21</sup> Subanesthetic doses of lidocaine, the stated goal for opioid-sparing, block ectopic nerve discharge but not conduction. Because of its pharmacokinetic profile, the drug should be used with caution in the elderly, in patients with known hepatic or renal dysfunction or heart failure, or in patients taking drugs that interfere with the cytochrome P450 enzyme. A major concern is combining intravenous lidocaine with concomitant injection of liposomal bupivacaine into abdominal fascial planes for pain control.<sup>13</sup>

**Table. Dose-Dependent Effects of Lidocaine**

Plasma Level, $\mu\text{g/mL}$	Effect
1-5	Analgesia
>5-10	Circumoral numbness Tinnitus Skeletal muscle twitching Hypotension Myocardial depression
>10-15	Unconsciousness Seizures
>15-25	Apnea Coma
>25	Cardiovascular collapse

The 2 drugs are amide local anesthetics with a similar structure. The transverse abdominis plane block is performed with a large volume of bupivacaine, up to 50 cc. Elevated plasma levels of both drugs may lead to immediate cardiac toxicity.

### Dexmedetomidine

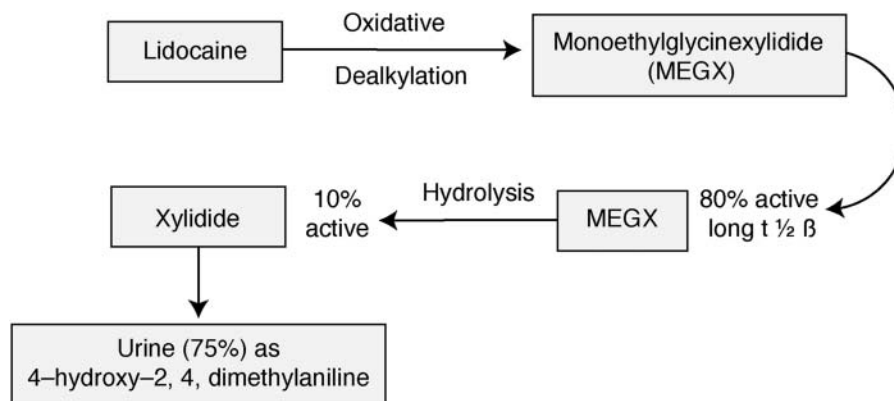
Dexmedetomidine is an alpha-2 agonist that has hypnotic, sedative, and analgesic properties<sup>22</sup> and is estimated to be 7-10 times more potent than clonidine.<sup>23</sup> Compared to clonidine, dexmedetomidine is a full, rather than a partial, agonist and highly selective and specific for the alpha receptor. The drug is protein bound, and like lidocaine, is metabolized in the liver with subsequent renal excretion.<sup>23</sup> Usually administered by continuous infusion, dexmedetomidine provides hypnosis and sedation and has analgesic properties. Pretreatment with dexmedetomidine attenuates the adrenergic response to tracheal intubation<sup>24</sup> and decreases plasma catechol concentrations during anesthesia; infusing dexmedetomidine results in a decrease in minimum alveolar concentration (MAC) for volatile anesthetic agents and has an opioid-sparing effect.<sup>22,25</sup> The analgesic effect is dose-dependent with little or no depression of ventilation. Loading doses of dexmedetomidine to rapidly reach the desired therapeutic effect may cause hypotension.<sup>26</sup> Dexmedetomidine attenuates the cardiostimulatory effects and postanesthetic delirium induced by ketamine.<sup>27</sup>

### Ketamine

Ketamine is a phencyclidine that was originally demonstrated to have a specific effect on N-methyl-D-aspartate receptors in the brain, a mechanism of action quite different than other anesthetic agents.<sup>28</sup> The drug has since been demonstrated to have a more distributive effect in other parts of the brain (thalamus and limbic systems) and analgesic effects that are mediated at the level of the spinal cord.<sup>28</sup> Ketamine is an amnesic and provides intense analgesia.<sup>28</sup> The analgesia is profound even at subanesthetic doses; at higher doses, ketamine is a complete anesthetic. Subanesthetic doses of ketamine reverse tolerance to opioids.<sup>29</sup> The drug exhibits extreme lipid solubility, rapid transfer across the blood-brain barrier, and a large  $V_D$ . The  $t_{1/2\beta}$  is 2-3 hours, but even so the drug has been successfully employed by continuous infusion.<sup>28</sup>

### Acetaminophen (Paracetamol)

Acetaminophen has a different mechanism of action than other analgesic drugs<sup>30</sup> but also has demonstrated analgesic and opioid-sparing properties.<sup>31</sup> In adults, the appropriate dose for preemptive analgesia is 1,000 mg administered intravenously for approximately 20 minutes.<sup>30</sup> The analgesic onset is rapid, within 5 minutes, but the peak concentration in plasma occurs at approximately 1 hour.<sup>32</sup> The duration of effect is 4-6 hours, and the  $t_{1/2\beta}$  is 2.0-2.5 hours.<sup>32</sup> Acetaminophen undergoes metabolism in the liver by conjugation with glucuronic and sulfuric acids; these conjugates are excreted in the urine.<sup>32</sup> Surgeons have embraced the use of intravenous acetaminophen, starting with a preoperative dose and repeating doses at 6-hour intervals.<sup>31</sup> Acetaminophen has been recommended in perioperative pediatrics for both analgesic and opioid-sparing effects.<sup>33,34</sup>



**Figure.** The diagram shows the metabolism of lidocaine and the comparative potency of active metabolites.

### Other Intravenous Analgesic Agents

Ketorolac is a nonsalicylate analgesic agent and nonsteroidal antiinflammatory drug (NSAID) that has desirable characteristics in managing postoperative pain.<sup>35</sup> Ketorolac mean plasma concentrations,  $V_D$ , and excretion are identical in healthy adults whether the dose is given by the intramuscular, intravenous, or oral route.<sup>36</sup> The pharmacokinetic profile of ketorolac in children is the same as in adults; the  $V_D$  and plasma clearance are identical.<sup>37</sup> The COX-1 and COX-2 mechanisms of action may play a role in inhibition of prostaglandin synthesis, resulting in anticoagulation at higher doses. For adult postoperative patients, a 15-30 mg intravenous dose of ketorolac, repeated once, has been shown to be safe and effective, and for pediatric patients, ketorolac in a dose of 0.5 mg/kg (maximum dose 30 mg) is similarly safe and effective.<sup>37</sup>

Ibuprofen, another NSAID with established analgesic and antipyretic properties, is approved by the US Food and Drug Administration for intravenous administration.<sup>38</sup> Doses of 400 mg and 800 mg have been shown to have an analgesic and opioid-sparing effect in postoperative patients.<sup>39</sup> Smith and Voss have shown that shortening the recommended 30-minute infusion time is both safe and effective.<sup>39</sup>

### AN OPIOID-FREE ANESTHETIC PRESCRIPTION

Based on evidence of drug action and interaction, an opioid-free anesthetic can be delivered with infusions of lidocaine (0.03 mg/kg/min), dexmedetomidine (0.5 mcg/kg/hr), and 0.5 MAC isoflurane. For procedures of less than 2 hours' duration, a bolus dose of lidocaine and dexmedetomidine can be considered. For procedures greater than 2 hours, no bolus dose is necessary.

#### Preoperatively

Administer acetaminophen 1,000 mg intravenously over 10-20 minutes. Give midazolam 1-2 mg intravenously as needed for anxiolysis.

#### Anesthetic Induction

Begin intravenous lidocaine infusion (0.03 mg/kg/min) and dexmedetomidine infusion (0.5 mcg/kg/hr) after monitors are in place. Induce anesthesia with propofol (1-2 mg/kg)

given intravenously for 2 minutes and add 10-25 mg of intravenous ketamine.

#### Anesthetic Maintenance

Begin inhalational anesthetic (0.8-1.0 MAC) and titrate to a lower dose (0.5 MAC) as tolerated. Maintain the infusion of lidocaine (0.03 mg/kg/hr) and dexmedetomidine (0.5 mcg/kg/hr). Reduce the infusion of dexmedetomidine to 0.25 mcg/kg/hr at 2 hours and discontinue 30 minutes prior to anesthetic emergence. At any time during anesthesia, but prior to emergence, ondansetron and dexamethasone can be given intravenously to prevent postoperative nausea.

#### Anesthetic Emergence

Decrease lidocaine infusion to 0.02 mg/kg/min at the time of emergence and to 0.015 mg/kg/min at the time of admission to the postanesthesia care unit (PACU). Use intravenous NSAIDs as the first choice for analgesia in recovery.

An Intralipid infusion should be immediately available for use in the operating room and the PACU if local anesthetic toxicity is suspected.<sup>40-42</sup>

### OPIOID-FREE ANESTHETIC CASES

We present a perioperative surgical patient and a preprocedural patient who underwent the opioid-free anesthetic technique with a successful outcome, adequate pain management, and avoidance of opioid drugs.

#### Patient 1

A 43-year-old female underwent bariatric surgery outside of the United States. Within 2 weeks after her return home, she presented to her primary care physician who diagnosed small bowel obstruction. She was referred for exploratory laparotomy, resulting in resection of dead bowel, and she was taken to the surgical intensive care unit with an open abdomen, the bowel in discontinuity, and an ileostomy. She subsequently became septic and developed acute respiratory distress syndrome. She required an extended period of mechanical ventilation, antibiotic therapy, and hemodynamic support. After 2 months in the hospital, she was transferred to a local long-term acute care facility for further recovery.

The patient presented 6 months later for takedown of the ileostomy and bowel anastomosis. During the preoperative interview, she requested that no narcotics be administered during or after her surgery because of her struggle to be opioid-free following her recent episode. We implemented the opioid-free anesthetic plan to honor the patient's request.

The surgical procedure was more difficult than anticipated because of adhesions, and the anesthetic time was 4.1 hours. The patient was extubated in the operating room.

At the time of admission to the PACU, the patient's lidocaine infusion at 0.015 mg/kg/hr was maintained; she appeared sedated but responded to commands and was oriented. On examination, she was warm and dry, with excellent pulses and good peripheral perfusion. Vital signs were normal except for blood pressure of 98/60 mmHg (her preoperative blood pressure was 132/80 mmHg). Other vital signs were pulse of 68 bpm, respiratory rate of 23 breaths per min, and oxygen saturation of 98% on room air. With fluid resuscitation, her blood pressure increased to 108/62 mmHg. She was discharged from the PACU after a 4-hour stay with vital signs within normal limits.

During her stay in the PACU, the patient was given one 30-mg dose of intravenous ketorolac for pain, and she was discharged with a visual analog pain score of 3/10. The lidocaine infusion was discontinued at the time of PACU discharge. Bowel sounds returned on the afternoon of the first postoperative day, and the patient began a clear liquid diet and was mobilized. She was discharged on the second postoperative day on oral acetaminophen and ibuprofen. She received no narcotics during her hospital stay.<sup>43</sup>

## Patient 2

A 44-year-old male with a diagnosis of chronic pancreatitis presented to the emergency department with acute on chronic pancreatitis and intractable abdominal pain, with little response to large doses of narcotics. The plan was to perform endoscopic retrograde cholangiopancreatography (ERCP) with possible stent placement. The patient was brought to the holding area, routine monitors were placed, and a lidocaine infusion was begun at 0.03 mg/kg/min following a 1.5 mg/kg bolus. Dexmedetomidine infusion of 0.5 mcg/kg/hr was also started with no initial bolus. After 2 hours, the patient's pain began to subside. At 4 hours, anesthesia was induced with intravenous propofol 2 mg/kg and 25 mg ketamine intravenously; anesthesia was maintained with the infusions of lidocaine and dexmedetomidine and inhaled isoflurane. A stent was successfully positioned during ERCP. Dexmedetomidine was discontinued prior to anesthetic emergence. The patient was successfully extubated; the lidocaine infusion was decreased to 0.015 mg/kg/hr and continued for 24 hours. Postprocedure, the patient received 1,000 mg of intravenous acetaminophen; further scheduled doses of acetaminophen were given by mouth (1,000 mg every 6 hours). He was discharged on the second postprocedural day, on no narcotics, with resolution of his pain postprocedure.

## CONCLUSION

The opioid epidemic in the United States is a complex issue with biochemical, sociologic, and behavioral factors. The availability of synthetic opioids and the increase in illegal distribution must be addressed. Prescribing habits

must be analyzed and altered to balance the obligation to adequately treat pain without subjecting patients to the possibility of addiction because of overprescribing.

We know that the incidence of new persistent opioid use following surgery and medical procedures is contributing to addiction. As an alternative to opioid anesthetic regimens, we present a multimodal approach to anesthetic care that works through the interaction of subanesthetic doses of intravenous agents; the mainstay of our anesthetic technique is infusing lidocaine and dexmedetomidine.

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