Perioperative Nonopioid Analgesic Adjuncts

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Disclosures

● No relevant financial disclosures
● Some medications are off-label when used for analgesic indications, but have been extensively studied.
  ● Gabapentin, pregabalin, dexamethasone, ketamine, magnesium, lidocaine, esmolol, dexmedetomidine
Perioperative Pain Management?

IT'S KIND OF A BIG DEAL!
Koepke EJ, Manning EL, Miller TE, Ganesh A, Williams DGA, Manning MW. The rising tide of opioid use and abuse: The role of the anesthesiologist. Periop Med. 2018; 7(16).
The Evolving Approach to Analgesia

Fig. 3. Pharmacologic approaches to perioperative management of the patient with medication-assisted treatment for substance abuse disorders. IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; PO, orally; PR, per rectum.
Table 2. Common Regional Analgesic Techniques

<table>
<thead>
<tr>
<th>Techniques</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuraxial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidural</td>
<td>Less pain (vs systemic opioids); reduced cardiac/pulmonary morbidity; earlier return of GI tract function; catheter use can continue into the postoperative period</td>
<td>Epidural LA: hypotension; sensory deficits; motor weakness; urinary retention</td>
</tr>
<tr>
<td>Spinal/intrathecal</td>
<td>Less pain; reduced systemic opioid requirements</td>
<td>Nausea; vomiting; pruritus; respiratory depression</td>
</tr>
<tr>
<td>Peripheral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAP block</td>
<td>Less pain; reduced systemic opioid requirements in the immediate postoperative period; typically performed under ultrasonographic guidance</td>
<td>Visceral pain; LA toxicity; perforation of the peritoneum with possible damage to visceral structures</td>
</tr>
<tr>
<td>Paravertebral block</td>
<td>Less pain; reduced systemic opioid requirements; lower risk of pulmonary complications for patients undergoing thoracotomy; catheter use can continue into the postoperative period; comparable levels of analgesia as epidural analgesia; less hypotension</td>
<td>Possible hypotension; vascular or pleural puncture; possible pneumothorax</td>
</tr>
<tr>
<td>Brachial plexus, sciatic/femoral nerve block</td>
<td>Less pain (vs systemic opioids); reduced systemic opioid requirements; catheter use can continue into the postoperative period</td>
<td>Not useful for abdominal or thoracic surgery; LA toxicity</td>
</tr>
<tr>
<td>Wound infiltration</td>
<td>Less pain and morphine consumption within the first few hours after surgery; easily administered by the surgeon</td>
<td>Uncertain long-term (≥24 h) analgesic efficacy</td>
</tr>
</tbody>
</table>
Preoperative Analgesics

● NSAIDs
  ○ Selective: celecoxib
  ○ Nonselective: ibuprofen, ketorolac, indomethacin, naproxen, diclofenac, nabumetone

● Acetaminophen

● Gabapentanoids
  ○ Gabapentin, pregabalin

● Dexamethasone
Gabapentin

Pregabalin

Dexamethasone

Nonopioid Analgesic Infusions

- Ketamine
- Magnesium
- Lidocaine
- Esmolol
- Dexmedetomidine
- Naloxone

Ketamine


Tissue Injury

↑ Glutamate release by primary nociceptive afferent in dorsal horn

Ketamine

- Enzymatic cascade
- Altered gene expression

Dorsal horn

NMDA receptor

Opioid receptor

Opioid

Central sensitization

Opioid tolerance

Opioid-induced hyperalgesia

Figure: Diagram illustrating the effect of ketamine on tissue injury and pain pathways.
TABLE 4. A Summary of Results of Systematic Reviews and Meta-Analyses on the Role of Ketamine as an Adjunct for Perioperative Analgesia

<table>
<thead>
<tr>
<th>Authors and Year</th>
<th>No. RCTs Included</th>
<th>Goal of Study</th>
<th>Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laskowski et al(^2) (2011)</td>
<td>70</td>
<td>Determine the effect of IV ketamine on postoperative analgesia</td>
<td>Ketamine reduced pain scores and opioid consumption; greatest efficacy in thoracic, upper abdominal, major orthopedic surgeries</td>
<td>Effect independent of type of intraoperative opioid, dose, or timing of ketamine Hallucinations and nightmares more common with ketamine</td>
</tr>
<tr>
<td>Jouguelet-Lacoste et al(^3) (2015)*</td>
<td>39</td>
<td>Determine the effect of an IV single dose or infusion of ketamine on postoperative analgesia</td>
<td>Ketamine reduced pain scores and opioid consumption for the first 48 postoperative hours</td>
<td>Evaluated a low-dose infusion rate of less than 1.2 mg/kg per hour with or without bolus dose of 1 mg/kg</td>
</tr>
<tr>
<td>Wang et al(^4) (2016)</td>
<td>36</td>
<td>Determine the effect of IV ketamine added to opioid IV-PCA</td>
<td>Ketamine reduced pain scores, opioid consumption, and PONV in the first 72 postoperative hours</td>
<td>Adverse events of ketamine were probably underreported</td>
</tr>
<tr>
<td>Assouline et al(^4) (2016)</td>
<td>19</td>
<td>Determine the effect of ketamine added to an opioid IV-PCA in surgical patients</td>
<td>Ketamine reduced pain scores, opioid consumption and PONV at 24 hours.</td>
<td>No significant change in the incidence of hallucinations. Data insufficient to draw conclusions on respiratory adverse events or a dose-response relationship.</td>
</tr>
<tr>
<td>Pendi et al(^5) (2018)</td>
<td>14</td>
<td>Determine the effect of ketamine on analgesia after spine surgery</td>
<td>Ketamine reduced pain scores and opioid consumption for the first 24 postoperative hours</td>
<td>No increase in adverse effects with ketamine</td>
</tr>
</tbody>
</table>

*Evidence-based review.
PONV indicates postoperative nausea and vomiting.

ASRA/AAPM/ASA Consensus Guidelines

● Who benefits?
  ○ Pts undergoing surgery with severe postoperative pain expected
  ○ Pts already opioid tolerant/dependent or with an acute exacerbation of chronic condition
  ○ Pts at risk for opioid-induced respiratory depression

● How much?
  ○ 0.3-0.5mg/kg +/- 0.1-0.5mg/kg/hour infusion per guidelines (Grade C level rec)

● When to avoid?
  ○ Poorly controlled CV disease, hepatic dysfunction, elevated IOP or ICP, hx psychosis, pregnancy

Ketamine Beyond the OR

- Decreased opioid consumption when compared to placebo when continued postoperatively with no significant change in side effects.

<table>
<thead>
<tr>
<th>Table 4. Postoperative Side Effects Between Day 0 and Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo (N = 75)</strong></td>
</tr>
<tr>
<td><strong>Risk for PONV according to Apfel score</strong> &lt;sup&gt;19,20&lt;/sup&gt; (%)</td>
</tr>
<tr>
<td>Patients receiving ondansetron at Day 1 (%)</td>
</tr>
<tr>
<td>Patients receiving ondansetron at Day 7 (%)</td>
</tr>
<tr>
<td>PONV described by patients at Day 7 (%)</td>
</tr>
<tr>
<td>Nausea from Day 0 to Day 7 (%)</td>
</tr>
<tr>
<td>Vomiting from Day 0 to Day 7 (%)</td>
</tr>
<tr>
<td>Pruritus (%)</td>
</tr>
<tr>
<td>Trouble with vision (%)</td>
</tr>
<tr>
<td>Urinary retention (%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nightmares (%)</td>
</tr>
<tr>
<td>Pleasant dreams (%)</td>
</tr>
<tr>
<td>Hallucinations (%)</td>
</tr>
</tbody>
</table>

Table 6. Ketamine Effect Stratified According to Preoperative Morphine Use

<table>
<thead>
<tr>
<th>Stratified by Preoperative Morphine Equivalent</th>
<th>Treatment</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (mg)</td>
<td>SD</td>
</tr>
<tr>
<td>≥0.556 mg/hr intravenously</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hr ME</td>
<td>17</td>
<td>168.8</td>
<td>94.4</td>
</tr>
<tr>
<td>48-hr ME</td>
<td>16</td>
<td>241.3</td>
<td>145.7</td>
</tr>
<tr>
<td>&lt;0.556 mg/hr intravenously</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hr ME</td>
<td>34</td>
<td>129.3</td>
<td>73.8</td>
</tr>
<tr>
<td>48-hr ME</td>
<td>33</td>
<td>172.7</td>
<td>83.2</td>
</tr>
</tbody>
</table>

ME = morphine equivalent.
Magnesium

- 2nd most common intracellular ion
- NMDA antagonism is mechanism of analgesia


De Oliveira et al Meta-analysis

- 30-50mg/kg bolus followed by 10-25mg/kg/hr
- 20 studies, 1257 patients
  - Cases included cardiothoracic, open abdominal, orthopedic/spine and endocrine

Albrecht et al Meta-analysis

- 25 trials, 1461 patients
  - Cases included abdominal, gynecologic, and orthopedic surgeries
  - Various protocols including bolus (30-50 mg/kg), bolus + infusion (6-25 mg/kg/hr), or infusion alone
- No correlation with total dose or protocol followed and cumulative opioid use
- Decreased morphine consumption occurred within the first 24 hours, but not beyond
- Very small decreases in postoperative pain scores (4-9/100)

Is Mg2+ supplementation all that is necessary?
Lidocaine

- Short-acting, amino-amide local anesthetic with analgesic, antihyperalgesic and anti-inflammatory properties
Koppert et al RCT in Major Abdominal Surgeries

- 40 patients without chronic pain history undergoing major abdominal surgery
  - Study arm received 1.5mg/kg bolus post-induction, 1.5mg/kg/hr infusion pre-incision, and continued until 60 minutes after closure.

Cochrane Review on Continuous IV Lidocaine

- 68 trials in 2017 update
  - Open abdominal, lap abdominal, and other surgeries; Most included 1.5 mg/kg bolus followed by 1-5mg/kg/hr started before incision with termination at end of surgery up to several days
- Small decrease in pain scores at rest with IV lidocaine in early postop (1-4 hrs) and intermediate period (24 hrs), but not late (48 hrs)
- Decreased intraoperative, early postop and overall opioid consumption
- Small decrease in incidence of ileus and time to first flatus and first bowel movement
- Shortened length of stay, higher patient satisfaction, decreased nausea (no difference in vomiting)

Limitations

- Ideal versus actual body weight?
- Route of administration? Thoracic epidural analgesia still preferable to IV lidocaine infusion if possible.

Esmolol

- Short-acting beta$_1$-receptor antagonist that is rapidly metabolized by plasma esterases
- Rat models suggest that the sympathetic blockade from esmolol may attenuate the inflammatory response to pain

Gelineau et al. Systematic Review and Meta-Analysis

- 23 RCTs including 1339 patients
  - 6 laparoscopic gynecologic, 8 laparoscopic abdominal, 2 unspecified abdominal, 3 orthopedic, 2 hernia repair, 2 septorhinoplasty and 1 total abdominal hysterectomy studies
- Esmolol regimen: 0.5-1mg/kg bolus followed by 0.5-50 mcg/kg/min infusion

Dexmedetomidine

- Alpha-2 adrenergic agonist, more selective than clonidine
- Sedative, sympatholytic and analgesic activity with minimal respiratory depressant effects

Singh et al Meta-Analysis

- 6 trials with 362 patients undergoing bariatric surgery
  - Protocols ranged from no bolus to 1 mcg/kg and infusions from 0.2 to 0.8 mcg/kg/hr, some occurring intraoperatively, some only postoperative

Cochrane Review

- 7 trials including 492 patients all undergoing abdominal surgery
  - 0.5-1 mcg/kg bolus followed by 0.2-0.8 mcg/kg/hr
- Modest reduction in 3 and 24 hour morphine consumption in dexmedetomidine group
- Clinically insignificant decrease in pain scores

Postoperative

- Continue Acetaminophen, NSAIDs, Gabapentinoids?
- Can continue some perioperative infusions (ketamine, lidocaine, dexmedetomidine)
- Consider alternative modalities
  - TENS units, massage, acupuncture, capsaicin, hot/cold packs, pet therapy, aromatherapy, distraction, meditation
### Scheduled Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Preop Dose</th>
<th>Postop Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>650-1000mg</td>
<td>650-1000mg q6-8h</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400-800mg</td>
<td>400-800mg q6-8h</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>400mg</td>
<td>200mg BID</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>15-30mg IV</td>
<td>15mg q6h IV</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300-600mg</td>
<td>300-1200mg q8h</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>100-300mg</td>
<td>150mg BID</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>7-10mg intraoperatively</td>
<td></td>
</tr>
</tbody>
</table>
### Intraoperative/Postoperative Infusions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Bolus Dose</th>
<th>Infusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>0.3-0.5 mg/kg post-induction</td>
<td>0.1-0.5 mg/kg/hr intraoperatively 10-12 mg/hr postoperatively</td>
</tr>
<tr>
<td>Magnesium</td>
<td>30-50 mg/kg bolus</td>
<td>10-25 mg/kg/hr *Limited evidence for benefit of infusion</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>1.5 mg/kg bolus post-induction</td>
<td>1-2 mg/kg/hr *Based on ideal body weight</td>
</tr>
<tr>
<td>Esmolol</td>
<td>0.5-1 mg/kg post-induction</td>
<td>0.5-50 mcg/kg/min *Limited evidence for benefit</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>0.5-1 mcg/kg bolus *Infuse over 10 minutes</td>
<td>0.2-0.8 mcg/kg/hr *Can continue into early PACU stay</td>
</tr>
<tr>
<td>Naloxone</td>
<td>No bolus</td>
<td>0.25 mcg/kg/hr</td>
</tr>
</tbody>
</table>


