Pain Infusions in the Perioperative Setting
Kristin Bevil, MD
Assistant Professor
Department of Anesthesiology
University of Wisconsin-Madison

Disclosures

- No relevant financial disclosures
Nonopioid Analgesic Infusions

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


Ketamine

- Noncompetitive NMDA antagonist as primary mechanism; also has mu-opioid, muscarinic, monoaminergic, GABA effects


Gorlin AW, Rosenfeld DM, Ramakrishna, H. Intravenous sub-anesthetic ketamine for perioperative analgesia. J Anaesthesiol Clin

ASRA/AAPM/ASA Consensus Guidelines

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

*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)
    - Pendi et al in meta-analysis found benefit for up to 24 hrs after spine surgery, but dosages varied 0.15-10mg/kg bolus and 0.06-5mg/kg/hr infusions

- **When to avoid?**
  - Poorly controlled CV disease, hepatic dysfunction, elevated IOP or ICP, hx psychosis, pregnancy based on relative contraindications for anesthetic dosages, but minimal study of subanesthetic ketamine in any of these populations


---

Ketamine Single-Bolus vs Infusion

- Morphine consumption and pain scores were significantly lower when a pre-incision bolus was followed by an infusion or when ketamine bolus occurred at wound closure.
- Morphine consumption was lowest when ketamine bolus was followed by an infusion.

Ketamine Beyond the OR

- Remerand et al; Adam et al: Decreased opioid consumption when compared to placebo when continued 24 to 48 hrs postoperatively.


Ketamine in Opioid Tolerant Patients

- Loftus et al - 102 patients undergoing major spine surgery
  - On sub-group analysis, in those patients taking at least 40 mg ME daily prior to surgery, there was a reduction of 230 mg of ME compared to placebo over 48 hours. However, there was no difference in ME consumed in the ketamine versus placebo arms for patients consuming < 40 mg of ME prior to surgery.

<table>
<thead>
<tr>
<th>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


DeOliveira et al Meta-analysis

- 30-50mg/kg bolus (2.8g for a 70kg man) followed by 10-25mg/kg/hr
- 20 studies, 1257 patients
  - Cases included cardiothoracic, open abdominal, orthopedic/spine and endocrine
  - Effects greater when administered both intra and postop compared to postoperatively alone

Albrecht et al Meta-analysis

- 25 trials, 1461 patients
  - Cases included abdominal, gynecologic, and orthopedic surgeries
  - Various protocols including bolus (30-50mg/kg), bolus + infusion, or infusion alone
- No correlation with total dose and cumulative opioid use, but cumulative morphine consumption decreased with magnesium use at 24hr regardless of administration method, but not beyond
- Very small decreases in postoperative pain scores (4-9/100)


Limitations

- Some studies that reported on Mag levels showed that control groups had decreased postoperative Mg levels, so unclear if Mg levels need to be corrected to normal or be slightly above normal to have analgesic effect
- No strong evidence for infusion over bolus if deciding to use Mag
- Inconsistent reporting on neuromuscular blockade
Lidocaine

- Short-acting, amino-amide local anesthetic with analgesic, antihyperalgesic and anti-inflammatory properties
  - Avoid in hepatic or renal insufficiency

Koeppert 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. Control received saline in equal volume.
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)


Vigneault et al Systematic Review

- 29 trials, 1754 total patients
  - 16 abdominal, 8 cardiac, 1 thoracic, 1 orthopedic, 1 obstetric, 1 tonsillectomy, and 1 ambulatory cases
  - Protocols typically included 1.5-2mg/kg bolus followed by 1.5-3mg/kg/hr infusion
Limitations

- The true benefits of lidocaine infusions may be the anti-hyperalgesic effect, which is hard to capture in most multimodal analgesic studies.
- Specific benefit may be in high inflammatory states, such as major abdominal surgeries.
- Thoracic epidural analgesia still preferable to IV lidocaine infusion if possible.


Esmolol

- Short-acting beta₁-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

Watts et al Systematic Review and Meta-Analysis

- 19 RCTs including 936 patients
  - 7 laparoscopic, 1 cardiac, 2 ENT, and 9 nonlaparoscopic abdominal or gynecological cases
- No discussion of control protocols
- Esmolol regimen: 0.5-1mg/kg bolus followed by 5-500 mcg/kg/min infusion


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
- Wide variability in protocols
  - Esmolol vs alfentanil or remifentanil infusion, vs scheduled fentanyl, inclusion of ketamine in control group. Esmolol was used alongside remifentanil in one study.
- 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

Bielka et al RCT

- 60 patients undergoing laparoscopic cholecystectomy
- Study arm received dexmed 0.5 mcg/kg/hr infusion from induction to emergence

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group D</th>
<th>Group C</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative morphine consumption (mg)</td>
<td>5 (0–10)</td>
<td>15 (10–20)</td>
<td>0.001²</td>
</tr>
<tr>
<td>Cumulative morphine consumption (mg)</td>
<td>15 (10–25)</td>
<td>30 (20–30)</td>
<td>0.001²</td>
</tr>
<tr>
<td>Severe pain incidence; n (%)</td>
<td>1 (3)</td>
<td>7 (23)</td>
<td>0.04¹</td>
</tr>
<tr>
<td>Time to first use of rescue analgesia (min)</td>
<td>180 (130–210)</td>
<td>80 (60–120)</td>
<td>0.001²</td>
</tr>
<tr>
<td>Time to extubation (min)</td>
<td>10 (5–10)</td>
<td>20 (15–20)</td>
<td>0.001²</td>
</tr>
<tr>
<td>Postoperative pain level (VRS score)</td>
<td>3 (3–4)</td>
<td>4 (4–5)</td>
<td>0.067²</td>
</tr>
<tr>
<td>6 h</td>
<td>4 (4–5)</td>
<td>3 (4–5)</td>
<td>0.08²</td>
</tr>
<tr>
<td>12 h</td>
<td>3 (3–3)</td>
<td>4 (4–5)</td>
<td>0.35²</td>
</tr>
<tr>
<td>24 h</td>
<td>4 (4–4)</td>
<td>4 (4–4)</td>
<td>0.72²</td>
</tr>
<tr>
<td>Intraoperative fentanyl consumption (mg)</td>
<td>0.5 (0.4–0.6)</td>
<td>0.6 (0.5–0.7)</td>
<td>0.03²</td>
</tr>
<tr>
<td>Persistent postoperative pain incidence; n (%)</td>
<td>1 (3)</td>
<td>10 (33)</td>
<td>0.005¹</td>
</tr>
</tbody>
</table>

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 in 2016; 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 with dexmedetomidine
- Sample size too small to evaluate secondary outcomes such as PONV, sedation, gastrointestinal function, and mobilization.

Cheng et al RCT evaluating Cognitive Dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasodrine n = 269</th>
<th>Saline n = 266</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to awake, min</td>
<td>17(17–25)1–623</td>
<td>17(10–25)2–570</td>
<td>0.92</td>
</tr>
<tr>
<td>Time to PACU awakening, min</td>
<td>5(11E–21.2)64</td>
<td>5(21E–21.2)59.2</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Delirium in recovery area

POCD

<table>
<thead>
<tr>
<th></th>
<th>14 (5%)</th>
<th>27 (10%)</th>
<th>0.03</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three days</td>
<td>40 (15%)</td>
<td>65 (24%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Seven days</td>
<td>31 (12%)</td>
<td>49 (18%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Cognitive impairment

<table>
<thead>
<tr>
<th></th>
<th>42 (17%)</th>
<th>61 (25%)</th>
<th>0.04</th>
</tr>
</thead>
<tbody>
<tr>
<td>One month</td>
<td>31 (13%)</td>
<td>34 (14%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Three months</td>
<td>16 (7%)</td>
<td>12 (5%)</td>
<td>0.56</td>
</tr>
</tbody>
</table>


Naloxone

- Mu-opioid selective antagonist; used perioperatively to treat acute opioid-induced respiratory depression or at ultra-low doses to address opioid side effects
- Opioid consumption may be decreased with low-dose infusions (0.25mcg/kg/hr) while higher doses (1mcg/kg/hr) likely require more opioid for equivalent analgesia. Both doses decrease the incidence of PONV and pruritus.


Conclusions

- Ketamine: improves analgesia; may be especially beneficial in chronic pain patients, but use with caution in patients with psychiatric illness.
- Magnesium: slightly improves analgesia, but unclear if necessary to supplement back to normal range or slightly above.
- Lidocaine: improves analgesia; may be especially beneficial in high-inflammatory states. Most research supports use in GI surgeries.
- Esmolol: May decrease intraoperative opioid use, but no evidence for prolonged effect postoperatively.
- Dexmedetomidine: improves analgesia; may be especially beneficial in patients at risk for respiratory complications and/or cognitive dysfunction.
- Naloxone: may decrease opioid consumption, but most support for decreasing opioid-induced nausea/vomiting and pruritis.

1. References

References Continued


