Table of Contents

Pharmacology

桄 The influence of propofol and sevoflurane on intestinal motility during laparoscopic surgery .......................................................... 3
桄 Efficacy of continuous S(+ ) ketamine infusion for postoperative pain control: a randomized placebo-controlled trial .................. 5
桄 Intravenous cosyntropin versus epidural blood patch for treatment of postdural puncture headache ...................................................... 8
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Pharmacology

**THE INFLUENCE OF PROPOFOL AND SEVOFLURANE ON INTESTINAL MOTILITY DURING LAPAROSCOPIC SURGERY**

Acta Anaesthesiol Scand 2016;60:335-42
Desmet M, Vander Cruyssen P, Pottel H, Carlier S, Devriendt D, Van Rooy F, De Corte W

**Abstract**

**Purpose** The purpose of this study was to compare the effects of propofol-remifentanil vs. sevoflurane-remifentanil on small bowel motility during laparoscopic surgery.

**Background** Small bowel motility can impair surgical conditions during complex bowel surgeries that require suturing or stapling. Choice of anesthesia can impact this motility. Bowel paralysis is a well-described effect of opioid administration, but there is limited information on the effects of volatile agents and intravenous agents. A previous investigation found that sevoflurane reduced peristaltic waves compared to desflurane through a reduction in tachykinin release; however, there is little information regarding the effects of propofol. Since propofol is the hypnotic agent of choice for induction and is used for maintenance of anesthesia, its effects on small bowel motility are of interest.

Intestinal motility is regulated by complex intrinsic and extrinsic motor pathways. A target of interest is the Transient Receptor Potential channel Ankyrin 1 (TRPA1), which is widely expressed throughout the intestinal system and increases gut motility when activated. In addition to potentiating GABA-A receptors in the brain, propofol activates TRPA1 at various locations throughout the body, including the gut. Therefore, it was hypothesized that propofol may contribute to increased motility through TRPA1 activation. As a first step toward investigating this relationship, the authors compared the effects of a sevoflurane versus propofol-maintained anesthetic on gut motility.

**Methodology** This was a prospective, single-blinded, randomized control trial of 50 adult, obese patients undergoing laparoscopic Roux en Y gastric bypass. The only exclusion criteria were cases considered redo surgeries. Patients were randomly assigned to groups prior to induction. The surgical team was blinded to the type of anesthesia. Following a propofol induction and non-depolarizing neuromuscular blockade, anesthesia maintenance was selected by study group. The “volatile” group (n=25) received sevoflurane with oxygen-enriched air. The “TIVA” group (n=25) received propofol maintenance via programmable pump. Both groups received a concurrent remifentanil infusion at similar doses between groups. Immediately prior to jejunojejunostomy, the surgeon and scrub nurse independently counted peristaltic waves for 1 minute while visually observing a specific 15 cm segment of the jejunum. If counts were different, the mean was calculated.
Result

There were no differences in patient demographics between groups (age, sex, BMI). There was no difference in total remifentanil dose or time to jejunum inspection between groups. In the TIVA group, a median of 6 peristaltic waves were counted compared to 0 waves in the volatile group (P<0.001). Total cumulative waves counted throughout all surgeries in the TIVA group was 149 compared to 38 in the volatile group. The type of anesthesia, propofol vs sevoflurane, was the only variable with a significant association to intestinal motility during surgery. Age, BMI, gender, remifentanil dose, and time until inspection of motility were not significantly associated with intestinal motility.

Conclusion

Maintaining general anesthesia with sevoflurane resulted in significantly less small bowel motility than maintenance with a propofol TIVA anesthetic. Sevoflurane anesthesia is superior to propofol TIVA during intestinal cases.

Comment

Anesthesia providers may not consider small bowel motility a high priority when formulating their anesthesia plans. Typically, we tend to direct more attention to malignant hyperthermia history, cardiovascular, pulmonary, PONV history, and other considerations when electing for a TIVA versus volatile anesthetic. However, increased small bowel motility can adversely impair surgical conditions for some types of bowel surgeries and therefore be of great interest to our surgeon colleagues. Although this is one study with a small sample size, the authors presented preliminary evidence suggesting a propofol-based TIVA increases gut motility. It is important to note that the authors did not state if increased observed peristaltic wave activity negatively impacted surgery completion, but their point is well taken. Our choice of anesthetic may impact bowel surgical conditions, and communication with the surgical team is paramount to improve conditions and possibly limit complications for our patients.

Ken Radford, Ph.D.(c), MS, CRNA
Pharmacology

Efficacy of continuous S(+)-ketamine infusion for postoperative pain control: A randomized placebo-controlled trial

Anesthesiol Res Pract 2016, 6918327
Miziara LE, Simoni RF, Esteves LO, Cangiani LH, Grillo-Filho GFR, Paula AG

Abstract

Purpose This study evaluated the efficacy of continuous intraoperative infusion of ketamine for postoperative pain control following laparoscopic cholecystectomy. Primary anesthesia for the procedures was a target-controlled total intravenous anesthesia (TIVA).

Background Postoperative pain control is not only important to improve patient comfort but to reduce effects related to poor pain control such as nausea, vomiting, and length of hospital stay. Administration of potent opioids is associated with central sensitization to pain, which is a phenomenon known as opioid-induced hyperalgesia. Opioid-induced hyperalgesia involves an increase in nociceptive sensitization associated with opioids and is characterized by a paradoxical response to opioid administration. That is, a patient receiving opioids for the treatment of pain actually becomes more sensitive to some painful stimuli. Potent short-acting opioids such as remifentanil have been implicated in the development of opioid-induced hyperalgesia.

Remifentanil has been shown to activate N-methyl-D-aspartate (NMDA) receptors in the spinal cord dorsal horn, which facilitates a hyperalgesic response to painful sensory stimuli. Ketamine, a non-competitive antagonist at NMDA receptors, may prevent Opioid-Induced Hyperalgesia through inactivation of spinal cord NMDA receptors. Ketamine is prepared in two varieties: S(+) ketamine, which is principally used outside the United States and racemic (R- and S+) ketamine, which is mainly used in the United States. S(+) ketamine has 4-times the analgesic potency compared to R(-) ketamine but is also associated with more psychotomimetic side effects such as hallucination. Little is known regarding the efficacy of a S(+) ketamine infusion on postoperative pain control for patients who receive intraoperative TIVA that includes remifentanil.

Methodology This was a double-blind, randomized, placebo-controlled trial conducted in a large medical facility in Brazil. The investigation had 42 patients of both genders aged 18 years to 65 years and ASA Physical Status I or II who underwent laparoscopic cholecystectomy. Following venipuncture, all patients received parecoxib 40 mg IV [Editor’s Note: parecoxib is a COX-2 selective inhibitor used outside the U.S. and is in the same class as celecoxib]. Target controlled TIVA was induced with propofol and remifentanil. The S(+) ketamine group (KET, n = 21) received a continuous infusion at a dose of 0.3 mg/kg/hr. This ketamine dose was, for example, only 21 mg an hour in a 70 Kg patient. The placebo group (SAL, n = 21) received a continuous infusion of saline.
at the same dose. Postoperative analgesia was measured by a verbal numeric rating scale (VNS) from 0 to 10 over 12 hours. Postoperative pain was treated with morphine when the verbal numeric rating scale score was equal to or higher than 3. Pain scores were recorded in the PACU and at 4 and 12 hours after the end of surgery. The amount of morphine used during PACU stay, from PACU discharge to 4 hours, and from 4 to 12 hours after surgery, and overall morphine consumption were recorded.

**Result**

There were no differences in demographic data, duration of surgery, duration of anesthesia, time until awakening, or duration of stay between groups. Mean remifentanil consumption was lower in the KET group vs. SAL group; 0.170 vs 0.228 µg/kg/min respectively (P = 0.01). Mean propofol consumption was lower in the KET group vs SAL group; 72.2 vs. 84.9 µg/kg/min (P = 0.02). Median pain scores (verbal numeric rating scale) were significantly lower in PACU, at 4 hours, and 12 hours after surgery in the KET group (Table 1). There was no difference in morphine consumption between groups during PACU stay. The KET group consumed significantly less morphine after PACU discharge to 4 hours, from 4 hours to 12 hours, and cumulatively (Table 2). There were no differences between groups with respect to adverse effects such as nausea, agitation, or hallucination.

<table>
<thead>
<tr>
<th>Table 1. Median Pain Scores (Verbal Numeric Rating Scale)</th>
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<tr>
<td><strong>Ketamine Group</strong></td>
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<tr>
<td>PACU</td>
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<tr>
<td><strong>P &lt; 0.001</strong></td>
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<tr>
<td>4h after surgery</td>
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<td><strong>P &lt; 0.001</strong></td>
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<td>12h after surgery</td>
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<td><strong>P &lt; 0.001</strong></td>
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<th>Table 2. Mean Morphine Consumption (mg)</th>
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<tr>
<td><strong>Ketamine Group</strong></td>
</tr>
<tr>
<td>PACU</td>
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<tr>
<td><strong>P = 0.58</strong></td>
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<tr>
<td>PACU to 4 hours</td>
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<td><strong>P = 0.01</strong></td>
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<td>4 to 12 hours</td>
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<td><strong>P = 0.008</strong></td>
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<td>Cumulative Total</td>
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<td><strong>P = 0.006</strong></td>
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**Conclusion**

Continuous intraoperative infusion of ketamine at 0.3 mg/kg/hr following a target-controlled propofol-remifentanil TIVA provided significantly better postoperative pain control than placebo over the first 12 hours after laparoscopic cholecystectomy.

**Comment**

While we appreciate the perceived benefits of administering opioids to our patients during surgery, it is important that anesthesia providers understand potential adverse effects such as opioid-induced hyperalgesia that occur postoperatively. Previous investigations have established that remifentanil and other potent opioids induce opioid-induced hyperalgesia and result in greater opioid consumption postoperatively. Therefore, exploring modalities to prevent opioid-induced hyperalgesia, such as low-dose ketamine infusions, are important clinical tools.
This was a clean and simple two-group study but had some methodological limitations. First, remifentanil was begun prior to the ketamine infusions. Although the investigators still found positive results, I wonder if antagonizing NMDA receptors prior to opioid exposure would have resulted in a reduced opioid consumption in PACU. The current study found no difference. Second, I would prefer the investigators measure additional outcome measures such as length of stay in PACU, total time until discharge, and patient satisfaction scores. Reduced pain scores and morphine consumption are important, but I would also like to know if the intervention affected the patient’s satisfaction with care, reduced hospital costs, and impacted staff burden. Lastly, the time period of measurement (up to 12 hours after surgery) was very short in my opinion. The investigators could have easily conducted a telephone follow-up at 24 and 48 hours for the small sample size used in the study to more accurately assess an extended look at opioid-induced hyperalgesia through verbal numeric rating scale pain scores and opioid consumption after discharge.

I use ketamine infusions intraoperatively for cases that I anticipate will be painful and will require large doses of opioids, both intra and postoperatively. I typically bolus ketamine on induction prior to opioid exposure and run a low-dose infusion for the duration of the case. Therefore, this study was of great interest to me and provides additional evidence for intraoperative ketamine use.

Ken Radford, Ph.D.(c), MS, CRNA

A Review of Opioid Induced Hyperalgesia can be found in a Pain Physician article available at the following URL:

http://www.painphysicianjournal.com/current/pdf?article=MTOQ0Ng%3D%3D&journal=60

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.
Abstract
Purpose The purpose of this study was to evaluate the efficacy of IV cosyntropin (Cortrosyn) compared to epidural blood patch for treatment of a postdural puncture headache (PDPH).

Background Epidural Blood Patch is considered the gold standard for the treatment of PDPH. Unfortunately, treatment with an Epidural Blood Patch requires an experienced anesthesia provider to perform and has some contraindications (e.g., coagulopathies). Epidural Blood Patch has also been associated with development of severe back pain, cranial palsies, neurological deterioration, and postpartum seizures.

Other treatments such as epidural morphine, intravenous hydrocortisone, gabapentin, and sumatriptan have been shown to have some efficacy, but none have been found to be superior to Epidural Blood Patch. Cosyntropin, a synthetic analogue of adrenocorticotropin hormone (ACTH), has been shown to have some efficacy in small studies compared to placebo for the prevention or treatment of a PDPH. The proposed mechanism of action of cosyntropin includes stimulated endorphin release, anti-inflammatory action, fluid and electrolyte retention, as well as direct stimulation of cerebral spinal fluid production. The latter mechanism may explain the bimodal response seen with cosyntropin in previous research in patients with PDPH (early relief, followed by increased headache pain, then decreased on subsequent days).

This study sought to compare cosyntropin to an Epidural Blood Patch in patients who presented to an emergency department with a PDPH. The authors hypothesized no difference in efficacy would be found between Epidural Blood Patch and cosyntropin when used for treatment of a PDPH.

Methodology This was a prospective, randomized study of N = 28 patients presenting with a postdural puncture headache at two United States Navy Military Treatment Facilities from 2006 to 2013. Exclusion criteria included: pregnancy, congestive heart failure, signs of increased intracranial pressure, local infection at site, coagulopathy, or not being a suitable candidate based on the anesthesia provider’s judgment.

Patients in the Epidural Blood Patch group received one liter of IV normal saline over 1 hour, followed by an Epidural Blood Patch with 20 mL of autologous blood injected via an 18 g Touhy needle. Patients in the cosyntropin group received 500 mg of cosyntropin...
in one liter of normal saline over 1 hour. All patients remained in the supine position for one hour after treatment. Patients in the cosyntropin group could opt for an Epidural Blood Patch if pain persisted after their initial treatment.

Efficacy was evaluated prior to discharge and at 1 day, 3 days, and 7 days using a verbal numeric rating scale for pain and function related to their headache (0-10). A 0 represented no pain or impairment of function, and a score of 10 represented maximum pain and impairment of function related to the headache.

Statistical analysis was appropriate. A P < 0.05 was considered significant.

**Result** There were N = 28 patients randomized to either the Epidural Blood Patch group (n = 13) or the cosyntropin (n = 15) group. No significant differences in demographics were found between the two groups. In the majority of patients in both groups (77%) PDPH resulted from a diagnostic lumbar puncture with a 21 g Quincke needle. The remaining subjects were postpartum (n = 3 in each group; Table 1). In the cosyntropin group 27% (n = 4) of subjects received an Epidural Blood Patch between their first and third post-treatment days, with one patient receiving 2 Epidural Blood Patches.

Patients who received an Epidural Blood Patch had significantly lower headache pain and function scores on post-procedure day 1 (P < 0.001; Figures 1 and 2). However, no differences were found between the two groups on days 3 and 7. Within the Epidural Blood Patch group, headache pain scores were significantly lower on day 1 compared to pre-treatment. In the cosyntropin group, headache pain scores were significantly lower from day 1 to day 3 and on day 7 (P < 0.001). No differences were found between days 3 and 7 within either group. In the cosyntropin group, 60% of patients returned to the emergency department after their initial treatment complaining of headache pain compared to only 8% of the Epidural Blood Patch group (P < 0.001).

Patients in the cosyntropin group were more likely to require additional pain medications after receiving their treatment compared to the Epidural Blood Patch group (67% vs. 17%; P < 0.001). In the cosyntropin group, n = 4 received a blood patch, n = 2 acupuncture, n = 2 hydrocodone/acetaminophen, n = 1 hydromorphine, n = 1 oxycodone/acetaminophen, and n = 1 gabapentin. In the Epidural Blood Patch

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<th>Table 1. PDPH Characteristics</th>
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<td>Baseline Pain</td>
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<td>Baseline function</td>
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<tr>
<td>Nausea/Vomiting</td>
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<tr>
<td>Neck Stiffness</td>
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<tr>
<td>Symptom onset (days post puncture)</td>
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<td>Study treatment (days post puncture)</td>
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**, Note:** No statistical differences between groups.
group, n = 1 received a repeat blood patch and n = caffeine. No differences were found between the groups in the number of patients who received IV fluids, caffeine, non-steroidal anti-inflammatory drugs, or opioids.

**Conclusion**  
No differences were found in headache relief at days 3 and 7 after treatment with either an Epidural Blood Patch or 1,000 mg cosyntropin in 1 liter of normal saline. It may be reasonable to consider cosyntropin when an Epidural Blood Patch is contraindicated or an anesthesia provider is not available.

**Comment**  
PDPH can be debilitating. The gold standard treatment is an Epidural Blood Patch. However, an anesthesia provider is not always available, and some patients may have contraindications to an Epidural Blood Patch. Unfortunately, we do not have great alternatives. I found these results interesting, in that they suggest cosyntropin, with a few caveats, may be an option when a patient cannot receive an Epidural Blood Patch.

Specifically, cosyntropin, like an Epidural Blood Patch, appears to immediately cut the average headache pain in half, but, unlike an Epidural Blood Patch, the headache appears to come back the next day, although not as severe. Thereafter, it appears...
headache pain decreases to similar levels as with an Epidural Blood Patch. This bimodal response is speculated to be due to an increase in cerebral spinal fluid production. Or it could be that the headache is just getting better over time. This study cannot answer that question because it did not include a placebo group (which would be unethical).

So I would consider cosyntropin an option in a patient who cannot receive or does not want an Epidural Blood Patch. I might consider offering it if they return after an Epidural Blood Patch. I would counsel them that they may feel better immediately after, but that the headache may worsen the next day, then get better. I would ensure they have some analgesics available and continue to drink caffeine products and fluids.

**Dennis Spence, PhD, CRNA**

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.