Pharmacology

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1 Pharmacology CE credit.*

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This is the second of five issues by Dr. Mary Golinski about acute and chronic postoperative pain management.

* This program has been prior approved by the American Association of Nurse Anesthetists for 20 Class A CE credits; Code Number 1035464; Expiration Date 10/31/2020.
A COMPARISON BETWEEN INTRAVENOUS LIDOCAINE AND KETAMINE ON ACUTE AND CHRONIC PAIN AFTER OPEN NEPHRECTOMY: A PROSPECTIVE, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY

Saudi J Anaesth. 2017;11:177-184
DOI: 10.4103/1658-354X.203027


Abstract

Purpose The purpose of this study was to assess whether perioperative IV lidocaine and IV ketamine reduced postsurgical pain following open nephrectomy.

Background Surgical removal of the kidney, or nephrectomy, is performed to treat cancer and other debilitating kidney diseases. It is also for organ donation. Thousands of nephrectomies are performed each year in the USA. It is one of the most common procedures in the surgical specialty of urology. Nephrectomy can be performed either laparoscopically or as an open procedure. Pain after open nephrectomy is a significant problem related to the invasiveness of the procedure. Common open approaches are transperitoneal, which can be extended to a bilateral subcostal and thoracoabdominal incision, or extraperitoneal. The surgical approach for tumor removal depends on the size and location of the tumor, and the patient's habitus. Effective postoperative analgesia facilitates recovery and is important for the prevention of chronic surgical pain. Analgesic adjuncts are being sought as part of multimodal analgesia. Among them are the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine and the amide local anesthetic lidocaine. This research assessed whether either drug, used for open nephrectomy, would:

- reduce morphine use over the first 24 hours postop
- enhance recovery during the first 48 hours postop
- minimize opioid-induced side effects
- produce side effects of the study drugs

Additionally, it sought to assess whether either drug had an impact on chronic postsurgical pain.

Methodology This was a prospective, randomized, double-blind trial. A total of 63 patients who met the inclusion criteria of age ≥ 18 years, ASA physical class I or II, and who were scheduled for elective open nephrectomy were enrolled. Each patient was randomly assigned to one of three treatment groups:

- **Lidocaine Group**- IV bolus of lidocaine 1.5 mg/Kg during induction followed by an infusion of 1 mg/Kg/h intraoperatively and 24 hours postoperatively.
- **Ketamine Group**- IV bolus of 0.15 mg/Kg during induction followed by an infusion of 0.1 mg/Kg/h intraoperatively and for 24 hours postoperatively.
- **Control Group**- equal volume of normal saline during induction followed by an infusion intraoperatively and for 24 hours postoperatively.

General anesthesia was standardized for all participants. Intraoperative analgesics included fentanyl (3 µg/Kg) as needed, 1 g of IV acetaminophen, and 20 mg of IV nefopam 30
minutes prior to surgery end time [Editor’s Note: nefopam is a non-opioid, non-NSAID analgesic available outside the USA]. In the PACU, morphine sulfate was administered until a Visual Analog pain Scale (VAS) score was less than 3 out of 10. Following the PACU analgesic regimen, patients were instructed in the use of IVPCA morphine as needed (no basal infusion). If additional analgesia was needed, acetaminophen and nefopam was given.

The primary outcome measure was cumulative morphine use over the first 24 hours following surgery. It was recorded at five time periods:

- 0 - 1 hour
- 0 - 6 hour
- 0 - 12 hour
- 0 - 18 hour
- 0 - 24 hour

Several secondary outcomes were measured including morphine administered in the PACU, pain sores for the first 48 postoperative hours, adverse effects from opioids, hallucinations, and any signs of lidocaine toxicity. Additionally, return of bowel function and functional walking capacity on the fourth postoperative day and/or at discharge, were monitored. All participants were contacted by telephone three months postop and questioned about chronic pain using the Douleur Neuropathique 4 questionnaire.

**Result** A total of 60 patients were included in the final analysis, 20 in each group. Demographics were similar between groups as was intraoperative fentanyl administered. The mean dose of IV morphine given in the PACU was greater in the control group than either the lidocaine or ketamine groups (P < 0.001). The cumulative morphine dose during the first 24 hours after surgery was greater in the control group than either the lidocaine or ketamine groups (P< 0.05). Pain scores at rest and during coughing or movement in the first 48 hours post-surgery were lower in the lidocaine and ketamine groups than the control group (P<0.05). Additionally, pain scores were lower in the lidocaine group than the ketamine group during the first 12 hours postoperatively (P< 0.05).

In terms of secondary objectives, only IV lidocaine significantly reduced the incidence of PONV (P< 0.001). The lidocaine group also had a shorter mean time to return of bowel sounds and ability to tolerate a first meal (P < 0.05). Mobilization time and length of hospital stay were significantly shorter in the lidocaine and ketamine groups compared to control (P< 0.05). However, bowel function and walking capacity, was significantly better in the lidocaine group compared to ketamine (P < 0.05). Only the lidocaine group was associated with reduced pain three months after surgery as measured by the neuropathic pain questionnaire. No patient experienced hallucinations because of ketamine or signs of local anesthesia toxicity.

**Conclusion** Induction bolus doses followed by IV infusions of either lidocaine or ketamine perioperatively reduced the cumulative morphine consumption in the first 24 hours post-nephrectomy. Both drugs significantly reduced pain scores compared to placebo during the first 48 hours postoperatively when patients were resting and during ambulation and coughing. Lidocaine, however, was more efficacious in its analgesic effects compared to ketamine both during the first 12 hours and three
months postoperatively. Lidocaine was also associated with enhanced gut function and physical rehabilitation. Neither lidocaine nor ketamine caused any adverse reactions.

Comment
The detailed description provided by the authors outlining the theory behind the mechanism of action of both ketamine and lidocaine in reducing the pain response following surgery is worth reading all by itself. In my clinical experience and excluding ERAS protocols where lidocaine is routinely part of the algorithm, it appears that ketamine is gaining significantly more attention compared to lidocaine in reducing opioid consumption during the perioperative period. There is little evidence in the scientific literature that identifies techniques and/or drugs that prevent or minimize both acute and chronic postoperative pain. One important risk factor for the development of chronic pain after surgery, although inconsistently reported, is the degree of acute postoperative pain. While both lidocaine and ketamine significantly reduced opioid use and reduced pain scores compared to placebo in this research, I was surprised to learn that lidocaine was more efficacious than ketamine for preventing chronic neuropathic pain following nephrectomy. This is in contrast to previous systematic reviews. The incidence of chronic pain following open nephrectomy ranges from low (4%) to moderate (27%). Interpreted another way, more than a quarter of patients who have an open nephrectomy may develop chronic pain. This is not surprising considering the surgical trauma when performing radical and open nephrectomy procedures. In this study, only one patient in the lidocaine group had a score on the DN4 of 5, which was significantly less than the scores of patients in the control and ketamine groups.

Mary A. Golinski, PhD, CRNA

Note
The Douleur Neuropathique 4 questionnaire (DN4) consists of 10 items. Seven of the items are related to pain quality and three items are based on a clinical examination. The DN4 is one of the questionnaires useful in diagnosing neuropathic pain, defined by the American Chronic Pain Association as a complex, chronic pain state that is usually accompanied by tissue injury. With neuropathic pain, the nerve fibers themselves might be damaged, dysfunctional, or injured. These damaged nerve fibers send incorrect signals to other pain centers. The impact of a nerve fiber injury includes a change in nerve function both at the site of injury and areas around the injury.

The DN4 requires asking the patient to describe how the pain feels and physical examination whether there is reduced sensation to touch or pinprick (hypoesthesia), or whether light brushing causes pain (allodynia). The scale, widely used since 2005 because of its simplicity, evaluates neuropathic pain following central and peripheral neurological lesions but is also used for diagnostic purposes, allowing the clinician to determine if the pain is of neuropathic origin. The questionnaire has been well validated in many studies.

DN4 Instrument
Prolonged Perioperative Low-Dose Ketamine Does Not Improve Short and Long-Term Outcomes After Pediatric Idiopathic Scoliosis Surgery

Spine 2017;42:E304-E312
DOI: 10.1097/BRS.0000000000001772
Perello A, Artes D, Pascuets C, Esteban E, Ey Batlle A

Abstract

Purpose   The purpose of this study was to test the hypothesis that a combination of low dose ketamine and opioid during and following posterior fusion for scoliosis repair in children would reduce central sensitization both short term and long term. Specifically, the hypothesis was that a combination of ketamine and opioid would:

• reduced postop morphine use
• minimize opioid adverse effects
• speed recovery
• reduced hyperalgesia
• decreased chronic pain postop

Background   Posterior spinal fusion surgery for repair of idiopathic scoliosis in the pediatric population is associated with high postoperative analgesia requirements. This lengthy and complex procedure is linked to the development of prolonged postsurgical pain. Typically, the procedure is performed using motor and sensory evoked potential monitoring. This prohibits the use of volatile agents and nondepolarizing muscle relaxants. General anesthesia is therefore often maintained with infusions of propofol and the ultra short acting opioid remifentanil. Both these drugs facilitate immediate postoperative neurologic assessment. Current scientific evidence suggests an association between extensive tissue injury (surgery) and moderate to high dose intraoperative opioids with postoperative hyperalgesia. Hyperalgesia can be a predictor of prolonged postsurgical pain. Moderate to high dose opioids and tissue injury both produce sensitization of the central nervous system. This may be through the interaction between excitatory amino acids and N-methyl-D-aspartate (NMDA) receptors in spinal cord dorsal horn neurons. Ketamine is an NMDA receptor antagonist that prevents central sensitization. When coadministered with opioids, it may prevent opioid induced hyperalgesia. If hyperalgesia is minimized, the dose of opioids needed to manage postoperative pain should be reduced, and thus, fewer opioid associated adverse effects will occur.

Methodology   This study was a single-center, randomized, placebo-controlled, double-blind experimental design. After parental informed consent, 60 patients between the ages of 10 and 18 years with a diagnosis of idiopathic scoliosis undergoing posterior vertebral fusion, were assessed for eligibility. Participants were randomized into one of two groups:

• Ketamine group: 0.5 mg/Kg ketamine during anesthesia induction followed by 2 µg/Kg/min until 72 hours postop
• Placebo group: 0.9% saline in the same quantities and for the same time as ketamine group

A standardized anesthetic was used for all participants; induction with propofol and cisatracurium, propofol maintenance infusions 6-8
mg/Kg/h, and remifentanil infusion 0.3 µg/Kg/min. Monitoring included intraarterial and central venous pressure monitoring. Prior to emergence and extubation 150 µg/Kg of morphine was administered. The remifentanil infusion was stopped at the end of surgery and morphine IVPCA was started in both groups at a basal rate of 5 µg/Kg/h, a 20 µg/Kg bolus, and 5 minute lockout. All patients received IV acetaminophen 15/mg/Kg every six hours (maximum 1 gm). At 72 hours postop the ketamine infusion, saline infusion, and morphine background infusions were stopped. The IVPCA morphine was continued. Oral acetaminophen and naproxen was begun.

The primary outcome variable measured was postoperative morphine use during the entire hospital stay. Secondary outcome variables were:

- Numeric Rating Scale pain at rest & during cough
- incidence of PONV & pruritus
- dysphoria, hallucinations, nightmares, diplopia
- sedation (Ramsay scale)
- respiratory depression
- time to oral intake
- time to ambulation
- length of hospital stay

Central sensitization was assessed by mechanical stimulation of the area of secondary hyperalgesia using a calibrated von Frey hair at 72 hours after surgery. (Editor’s Note: von Frey hairs are described in more detail in the notes at the end of this abstract and comment.)

All participants were followed through hospital discharge and for 6 months after surgery. There were two in-person visits at six weeks & six months and a telephone assessment at three months. Pain was measured at these times both at rest and during movement. The Douleur Neuropathique 4 questionnaire was completed to assess neuropathic pain at six weeks and six months.

**Result** The final analysis was conducted on a total of 44 patients; 21 in the ketamine group and 23 in the placebo group. Of the demographic variables measured only BMI was notably different between groups. The placebo group mean BMI was 22.6 Kg/m² compared to 20.4 Kg/m² in the ketamine group.

Table 1 shows IVPCA morphine consumption during various time periods throughout the hospital stay. There were no statistically significant differences between the ketamine and control groups. The cumulative morphine consumption was also similar between groups.

<table>
<thead>
<tr>
<th>Table 1 - Morphine Consumption (mg/Kg)</th>
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<tbody>
<tr>
<td>Time Period</td>
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<tr>
<td>12 hours</td>
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<tr>
<td>24 hours</td>
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<tr>
<td>48 hours</td>
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<tr>
<td>72 hours</td>
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<tr>
<td>Cumulative</td>
</tr>
</tbody>
</table>

Notes: morphine mean (standard deviation). P = statistical P Value

There were also no statistically significant differences between the two groups for:

- Numeric Rating Scale pain at rest or during coughing
- PONV
- pruritus
- hallucinations, nightmares
- dysphoria or diplopia (none either group)
- sedation
- respiratory depression
- time to oral intake
- time to ambulation
- days in the hospital
There was no difference in central sensitization measured at 72 hours. Postsurgical pain measured at three and six months was no different between groups. The incidence of prolonged postsurgical pain at six months was slightly more than 19% in both groups. Those with pain at six months did not demonstrate hyperalgesia at 72 hours nor greater morphine consumption than those without prolonged postsurgical pain.

**Conclusion**
This study demonstrated no evidence that prolonged sub-anesthetic ketamine infusion reduced central sensitization or morphine consumption, offered greater pain relief, improved recovery, or reduced the incidence of prolonged postsurgical pain.

**Comment**
Opioid-induced hyperalgesia is defined as a state of nociceptive sensitization caused by exposure to opioids. A paradoxical response characterizes the condition whereby a patient receiving opioids for pain becomes hypersensitive to painful stimuli. We simply do not know why some develop hyperalgesia. Genetics certainly may play a role, as can complex physiologic and psychologic disturbances and even a chronic pain. Numerous clinical trials have shown that intraoperative use of moderate to high dose fentanyl class opioids, including remifentanil, is associated with development of hyperalgesia. In my clinical practice, remifentanil is frequently administered during complex spine procedures where sensory and motor monitoring prohibits other drugs and when immediate postoperative neurologic assessment is necessary. Ketamine, an NMDA receptor antagonist, has been used as an anesthesia adjunct, to prevent acute and chronic pain, and to prevent opioid induced hyperalgesia. Acute postoperative pain and hyperalgesia are risk factors in the development of prolonged postsurgical pain. The authors conducted this clinical trial on an underrepresented subset of the population who by nature of their diagnosis and subsequent surgery, are at very high risk for developing prolonged postsurgical pain. While the study had several limitations such as a wide age range (10-18 years), very low doses of ketamine, and a relatively small sample size that may have influenced the non-significant results, I applaud the effort. It is an impressive beginning to address a major public health issue that does not discriminate based on age.

**Mary A Golinski, PhD, CRNA**

**Notes**
What is a von Frey Filament?
https://en.wikipedia.org/wiki/Von_Frey_hair

**Ramsay Sedation Scale**
The scale scores sedation at six different levels.

1. Anxious & agitated or restless, or both
2. Cooperative, oriented, & tranquil
3. Responds to commands only
4. Exhibits brisk response to light forehead tap or loud auditory stimulus
5. Exhibits sluggish response to light forehead tap or loud auditory stimulus
6. Exhibits no response
Pharmacology

**INTRAOPERATIVE KETAMINE REDUCES IMMEDIATE POSTOPERATIVE OPIOID CONSUMPTION AFTER SPINAL FUSION SURGERY IN CHRONIC PAIN PATIENTS WITH OPIOID DEPENDENCY: A RANDOMIZED, BLINDED TRIAL**

Pain 2017;158:463-470
DOI: 10.1097/j.pain.0000000000000782

Neilsen RV, Fomsgaard JS, Siegel H, Martusevicius R, Nikolajsen L, Dahl JB, Mathiesen O

**Abstract**

**Purpose** The purpose of this clinical trial was to assess the effects of intra-operative ketamine on postoperative opioid consumption, acute pain, and persistent post-surgical pain. Secondary outcomes included adverse effects of morphine, adverse effects of ketamine, the incidence of hallucinations or nightmares in patients with a history of chronic opioid use, and pain six months after surgery.

**Background** Spinal fusion surgery results in significant postoperative pain. Typically, those who undergo spine surgery have been taking opioids for extended periods of time preoperatively. Many patients are have been experiencing chronic pain and may be opioid dependent. Previous research has identified this population as at high risk for opioid induced hyperalgesia. Ketamine attenuates both central sensitization (a condition of the nervous system associated with development of chronic pain) and hyperalgesia (hypersensitivity to certain painful stimuli) caused by opioid exposure. What is not completely understood is the efficacy of ketamine for management of acute pain and prevention of central sensitization in this high risk group. Also not well understood is the dose of ketamine needed to achieve these effects.

**Methodology** This was a single-center, prospective, randomized, and blinded, study. It included patients undergoing lumbar fusion with general anesthesia who had chronic back pain for more than three months and used opioids for more than six weeks. Additional inclusion criteria were ASA Physical Status I - III, age 18 – 85 years, and BMI between 18 - 40 Kg/m². Participants were randomized to one of two groups:

- **Ketamine group:** 0.5 mg/Kg ketamine bolus + 0.25 mg/Kg/hr
- **Placebo group:** normal saline after induction + infusion.

All patients received oral acetaminophen 1,000 mg one hour before surgery. General anesthesia was maintained with propofol, remifentanil, rocuronium, and the infusion of ketamine or placebo. Morphine 0.4 mg/Kg was administered intravenously 45 minutes before surgery completion. Study infusions were turned off as the last skin suture was placed. On emergence, if the patient exhibited excessive pain, 5 µg IV sufentanil was administered. Postoperatively, all patients received oral acetaminophen for 24 hours and IVPCA morphine.

**Results** A total of 147 patients were included in data analysis; 74 in the ketamine group and 73 in the
placebo group. Demographics were similar in both groups. The median \textit{preoperative} daily use of opioids, measured in morphine equivalents, was 60 mg in the ketamine group and 58 mg in the placebo group.

IVPCA morphine consumption during the first 24-hours \textit{postoperatively} was 35\% lower in the ketamine group than in controls; 79 mg versus 121 mg (P < 0.001). This amounts to 3.3 mg/h in the ketamine group vs. 5 mg/h in the control group. There was no significant difference in rescue IV morphine requirements between groups.

Acute Pain during the first 24 hours postop, at rest or during ambulation, was no different between groups despite significantly less IVPCA morphine use in the ketamine group. Sedation scores were significantly lower ketamine patients at postoperative hours 6 (P = 0.005) and 24 (P = 0.04). Postoperatively, the Low Back Pain questionnaire showed significantly less disability in the ketamine group compared to placebo (P = 0.006). Daily postoperative analgesic use was reported by 44\% of patients in the ketamine group compared to 62\% of control patients. The ketamine group was able to walk significantly longer distances compared to control patients (P = 0.01).

No significant differences were noted between groups for PONV, antiemetic requirements, hallucinations, or nightmares. Measurements of persistent post-surgical pain showed no differences for back pain or leg pain. There were no significant differences between groups in routine analgesic requirements. However, when participants were asked about their back pain compared to preoperative measurements, the ketamine group reported significantly greater improvements in back pain (P < 0.006).

An especially interesting side note was the post hoc analysis that examined the effect of ketamine on postoperative morphine use based upon the amount of \textit{preoperative} opioids consumed. Ketamine patients who had consumed $\geq 36$ mg of oral morphine equivalents a day preoperatively used 37\% less IVPCA morphine during the first 24 hours postoperatively than control patients who had previously used these high doses of morphine (P < 0.001). In contrast, ketamine patients who had consumed less than 36 mg of oral morphine equivalents a day preoperatively had no change in their IVPCA morphine use during the first 24 hours postoperatively.

\textbf{Conclusion} This study demonstrated that intraoperative low-dose ketamine significantly reduced IVPCA morphine consumption during the first 24 hours after lumbar fusion in patients who had used opioids routinely preop. Despite the reduction in postop opioid use in ketamine patients, there was no significant difference in pain scores. Participants who received ketamine nevertheless reported significant improvement of their back pain, walking distance, and total less disability at six months.

\textbf{Comment} The universally accepted definition of chronic back pain is pain that persists for 12 weeks or longer, even after the injury or underlying cause has been treated.
Approximately 20% of people who suffer from acute low back pain develop chronic low back pain with symptoms remaining one year later. In some the pain persists despite surgical treatment. In 1990, low back pain was ranked sixth for most burdensome conditions and in 2010 it ranked third. Spinal fusion surgery involves the stabilization of two or more vertebrae fused together with or without instrumentation. The expected outcome is an improved quality of life, relief of pain, and a stable spine. The current statistics are staggering. Nearly half a million spine surgeries are performed each year in the USA. Unfortunately, some patients become dependent on opioids prior to surgery. This of course complicates the anesthetic, recovery, and rehabilitation. According to a study published in 2015 the evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. However, we do know that evidence supports a dose dependent risk for serious harm. The greater the dose of opioids, the greater the incidence of acute and chronic postoperative pain, the potential for abuse, overdose, dependence, gastrointestinal complications, sleep-disordered breathing, hypothalamic-pituitary-adrenal dysregulation, an increased risk of bone trauma, an increased risk of myocardial infarction, and others. The result of chronic back pain is of course reflective of the volume of procedures performed and anesthetics we administer for spinal fusion surgery. As anesthesia and pain management experts, we seek to find answers to the question, “what is the best anesthetic for the population presenting for spinal fusion surgery?” This study investigated the utility of ketamine as an anesthesia adjunct that minimizes acute postoperative pain and opioid consumption.

The hypothesis was that an NMDA antagonist would minimize central sensitization and hyperalgesia, thereby reducing postoperative opioid tolerance and the chronic pain state. These investigators used a plethora of instruments. While at times it appeared overwhelming, I applaud them for enhancing reliability of results and not relying on any one tool to explain the all the outcomes. The greater the number of metrics, the closer we may be to understanding the best treatment. And in these adult spine surgery patients, the better treatment included intraoperative ketamine!

Mary A Golinski, PhD, CRNA

End Notes
