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Sedation with dexmedetomidine prolongs the analgesic duration of brachial plexus block: a randomized controlled trial

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Abstract
Purpose The purpose of this study was to determine if an IV infusion of dexmedetomidine resulted in a longer time to first patient analgesic request in patients who received a supraclavicular block for upper extremity surgery.

Background Brachial plexus block is commonly used to provide surgical anesthesia and extended postoperative analgesia for upper extremity surgery of the radius or ulna. Dexmedetomidine, an alpha-2 agonist, is a sedative with analgesic effects. Previous research comparing 0.5 µg/Kg of IV or perineural dexmedetomidine demonstrated that IV administration prolonged analgesia and reduced opioid consumption. However, no studies have been published comparing a clinical sedative dose of dexmedetomidine on analgesic duration after supraclavicular nerve block.

Methodology This was a prospective, randomized, controlled trial of ASA I-III patients aged 20 - 70 years who underwent open reduction and internal fixation for fractures of the radius or ulnar shortening surgery for ulnar impaction under supraclavicular nerve block with sedation. Patients were randomized to receive dexmedetomidine (bolus 1 µg/Kg over 10 minutes then 0.6 µg/Kg/hr until skin suture; Group D) or midazolam (3 mg if over 60 Kg and 2 mg if <60 Kg; Group M) for sedation during surgery. Level of sedation was monitored with a modified Ramsey Sedation Scale (mRSS). If additional sedation was needed, Group D infusion was increased to 0.7 - 0.8 µg/Kg/hr and Group M received 2 mg midazolam. No opioids were administered intraoperatively.

All patients received an ultrasound-guided supraclavicular block with 25 mL 0.5% lidocaine + 0.375% ropivacaine. Sensory block of the operative dermatome was confirmed prior to incision. Postoperatively all patients received IVPCA fentanyl (bolus 0.5 µg/Kg, lockout 10 minutes, max dose 1,000 µg, no basal rate). If pain was not controlled, meperidine 25 mg was administered. All patients received nefopam 20 mg every 12 hours [Editor's Note: nefopam is a non-opioid analgesic available in the UK and Australia].

The primary outcome was the time to first analgesic request, defined as the time from block placement to first bolus on the PCA. The secondary outcome was total opioid consumption during the first 24-hours. The investigators hypothesized that dexmedetomidine would increase the mean time to first analgesic request by 30%, so they estimated they needed 102 patients. Statistical analysis was appropriate. A P < 0.05 was significant.
**Result**  In Group D n = 49 and in Group M n = 47 completed the study. Demographics and clinical characteristics were similar. Patients in Group D received a median 96 µg (80 - 114 µg) dexmedetomidine. Group M received a median 3 mg (3 - 4.5 mg) midazolam. The median time to first analgesic request was significantly longer in Group D (10 hours 15 min) than Group M (7 hours 20 min) (P < 0.001). Dexmedetomidine prolonged the time to first analgesic by 28%.

Once patients began using IVPCA, the frequency of PCA use was similar between the groups; however, total fentanyl consumption was significantly lower in the dexmedetomidine Group (mean difference = 107 µg, P = 0.035). Frequency of rescue analgesics were significantly higher in Group M compared to Group D (75% vs. 45%, P < 0.001). Total opioid consumption (fentanyl & meperidine) was significantly lower in the dexmedetomidine Group (P = 0.01). Pain scores at first analgesic request (4 vs. 2, P = 0.001) and maximum pain scores (5 vs. 3, P < 0.001), were significantly higher in Group M compared to Group D. There was no difference in perioperative adverse effects between the groups.

**Conclusion**  Sedation with dexmedetomidine during upper extremity surgery under brachial plexus block with 0.5% lidocaine + 0.375% ropivacaine significantly prolonged the time to first analgesic request and reduced total opioid consumption during the first 24 hours.

**Comment**  So how does an intravenous infusion of dexmedetomidine prolong analgesia after a brachial plexus block? The mechanism of action is purported to involve spinal, supraspinal, direct action on nerves, and systemic effects. Centrally, dexmedetomidine directly affects alpha 2 adrenoreceptors of the locus coeruleus. Intravenous dexmedetomidine produces a greater degree of differential blockade by preferentially blocking unmyelinated C fibers involved in sensory conduction over myelinated A-alpha fibers involved in motor conduction.

The strengths of this study are that they confirmed the supraclavicular blocks were successful and used a PCA to objectively measure time to first analgesic request. This study was not designed to examine sensory block duration; therefore one cannot tell if the outcomes were due to systemic analgesic effects or potentiation of the nerve blocks. I would like to see future studies examine difference in brachial plexus block duration with perineural and IV administered dexmedetomidine.

**Dennis Spence, PhD, CRNA**

**NOTE:** See more on this topic in *Anesthesia Abstracts* issue 9.12.

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Predosing Chemical Stability of Admixtures of Propofol, Ketamine, Fentanyl, and Remifentanil

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Abstract

Purpose The purpose of this study was to compare the stability and concentrations remaining of mixtures of propofol and ketamine; propofol, ketamine, and fentanyl; or propofol, ketamine, and remifentanil at room temperature, 37°C, or while being constantly mixed for up to 24 hours.

Background Anesthesia providers deployed to austere settings often do not have an anesthesia machine. They often administer total intravenous anesthesia with a mixture of propofol and ketamine or propofol with ketamine and fentanyl. However, little is known about the chemical stability and concentrations of the individual drugs under conditions which may be seen on the battlefield in austere environments.

Methodology This was a laboratory experiment which subjected the following admixture of drug combinations to various conditions which may be seen on the battlefield:

A) 10 mg propofol (group P)
B) 10 mg propofol + 1 mg ketamine (group PK)
C) 10 mg propofol + 1 mg ketamine + 0.5 µg fentanyl (group PKf)
D) 10 mg propofol + 1 mg ketamine + 5 µg remifentanil (group PKr)

Samples were tested for chemical stability (% drug remaining) at 6 hours and 24 hours using high-performance liquid chromatography-mass spectrometry. Prior to testing the samples were stored at room temperature, at 37°C, or while being continuously rotated at room temperature to mimic being transported. At least 3 batches were performed on different days as replicate experiments to confirm results. The US Pharmacopeia standard for compounded medications is 90% to 110% concentration of labeled content.

Result The percent drug remaining of P, PK, and PKr at room temperature, 37 °C, and constant rotation were all >96% at 6 and 24 hours. The percents of PKf remaining were >99% when tested at room temperature and 37°C at 6 and 24 hours; however, with the PKf admixture at constant rotation for 24 hours, the propofol remaining was only 65% ± 29%, ketamine 99%, and fentanyl 84% ± 20% which suggested degradation of propofol and fentanyl (Figure 1). Concentrations of PKf at 6 hours after constant rotation were within acceptable ranges (>96%).

Conclusion All formulations retained acceptable concentrations under various conditions that may be seen on the battlefield. The exception was that PKf admixtures may degrade with constant mixing for a prolonged period of time.
Comment
This study is important to military anesthesia providers who deploy to austere environments to provide anesthesia for damage control surgery on the battlefield. Most of the time all they have to administer anesthesia is what fits in their backpack. So total intravenous anesthesia is often administered. Many times, these anesthesia providers will premix their medications, so knowing if the drugs concentrations are stable after prolonged storage and under various conditions is critically important. The results of this study fill that void and provide us with some reassurances that most admixtures of PK and PKr, and PKf are stable under most conditions. Concentrations may degrade with constant movement with an admixture of PKf. However, it is unlikely that an anesthesia provider would have these drugs premixed for such a long period of time.

I would like to see this study replicated at much higher temperatures, such as those seen in the desert. Replacing propofol with midazolam and rerunning these tests would provide valuable information since an admixture of midazolam, ketamine, and fentanyl is commonly used on the battlefield.

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.
INTRAVENOUS INFUSION OF LIDOCAINE SIGNIFICANTLY REDUCES PROPOFOL DOSE FOR COLONOSCOPY: A RANDOMISED PLACEBO-CONTROLLED STUDY

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Abstract

Purpose The purpose of this study was to determine if an intravenous bolus and infusion of lidocaine decreases propofol requirements during colonoscopy.

Background Propofol is the most common medication administered for sedation for colonoscopy. Unfortunately, closed claims studies indicate respiratory depression secondary to over-sedation is associated with patient morbidity and mortality. Some providers administer propofol and ketamine to reduce propofol requirements and improve endoscopy conditions and cardiopulmonary status. Intravenous lidocaine added to sedation with propofol and ketamine sedation for colonoscopy may further decrease propofol requirements and optimize outcomes. Lidocaine may reduce the visceral pain associated with colonic distention and traction during colonoscopy. Additionally, some studies indicate lidocaine increases ventilatory response to carbon dioxide; therefore, it may help reduce the rate of adverse respiratory events during colonoscopy.

Methodology This was a prospective, randomized, double-blind, placebo-controlled study. ASA 1-2 patients undergoing colonoscopy were enrolled. Patients were excluded if they were <18 or >70 yr, had a history of renal failure, liver insufficiency, epilepsy, major cardiac arrhythmia, or allergy to lidocaine. They were randomized to either an intravenous bolus of lidocaine and infusion (1.5 mg/Kg then 4 mg/Kg/hr) or placebo (saline bolus and infusion). Patients, anesthesia professionals, and gastroenterologists were blinded to group assignment. All subjects received a bolus of propofol 0.5 mg/Kg followed by additional 20-30 mg boluses to achieve unconsciousness during introduction of the endoscope. Then a bolus of ketamine 0.3 mg/Kg was administered. Next subjects received either the lidocaine bolus or a saline placebo followed by the infusion. During the procedure patients were allowed to recover to a level of consciousness to answer simple questions. Additional boluses of propofol 20-30 mg and ketamine 10 mg were administered as needed. Oxygen 4 LPM via nasal cannula was administered to all subjects.

The primary outcome was the total dose of propofol. Secondary outcomes were the frequency of oxygen desaturations <95%, pain scores after the colonoscopy, and endoscopist rating of exam conditions using a 0-10 cm visual analog scale. Personnel involved in the assessment of outcomes were blinded to group assignment. Sample size calculations and statistical analysis were appropriate. A P < 0.05 was considered significant.
Result There were 21 subjects randomized in each group, with one subject being excluded from the final analysis (N = 40, with n = 20 in each group). Baseline demographics were similar except for age. Subjects in the lidocaine group were significantly older compared to the saline group (median [IQR]: 59 [41-69] yr vs. 53 [25-65] yr, P = 0.03). Colonoscopy duration was similar (26 min. vs. 21 min., P = NS).

Subjects in the lidocaine group required significantly less propofol than those in the saline group (128 ± 53 mg vs. 200 ± 109 mg, P = 0.001). No differences in ketamine requirement was found (19 mg vs. 20 mg). Subjects in the lidocaine group received 188 ± 37 mg. The rate of oxygen desaturation <95% was 25% in both groups; the rate of desaturation <90% was 20% in the lidocaine group and 25% in the saline group. Colonoscopy condition ratings by the gastroenterologists were similar in the lidocaine and placebo groups (9.7 vs 9.1). Pain scores in the recovery room were significantly lower in the lidocaine group (P = 0.02).

Conclusion An intravenous bolus and infusion of lidocaine (1.5 mg/Kg then 4 mg/Kg/hr) decreased propofol requirements by 50% in patients undergoing colonoscopy with propofol and ketamine, without impacting endoscopy conditions.

Comment I provide sedation for a lot of patients undergoing colonoscopy, so I was interested in this study. The investigators found a lidocaine bolus and infusion (1.5 mg/Kg then 4 mg/Kg/hr) decreased propofol requirements during colonoscopy. I often give patients 20-30 mg bolus of lidocaine prior to administration of the propofol bolus. Based on these results I might consider administering a 1.5 mg/Kg lidocaine bolus.

However, at my center we do not have ketamine available nor do we have the ability to administer a lidocaine infusion. I would have liked to have seen this study have an additional group that only received a lidocaine bolus and not an infusion and been conducted without ketamine. This would have more realistically reflected clinical practice at endoscopy centers in the United States. I am not sure if a lidocaine infusion is value added since colonoscopies are often rather short procedures (<30 minutes).

A limitation of this study was that the lidocaine group were significantly older which may have biased the results. Nonetheless, I think the results provide us with an additional anesthetic technique to consider for colonoscopy.

Dennis Spence, PhD, CRNA

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