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Pharmacology

Intravenous subdissociative-dose ketamine versus morphine for acute geriatric pain in the Emergency Department: a randomized controlled trial

Am J Emerg Med 2018; (Published ahead of print)
DOI: 10.1016/j.ajem.2018.05.030

Motov S, Mann S, Drapkin J, Butt M, Likourezos A, Yetter E, Brady J, Rothberger N, Gohel A, Flom P, Mai M, Fromm C, Marshall J

Abstract

Purpose The purpose of this study was to compare the analgesic efficacy and safety of subdissociative-dose ketamine (SDK) for the treatment of acute pain in geriatric patients.

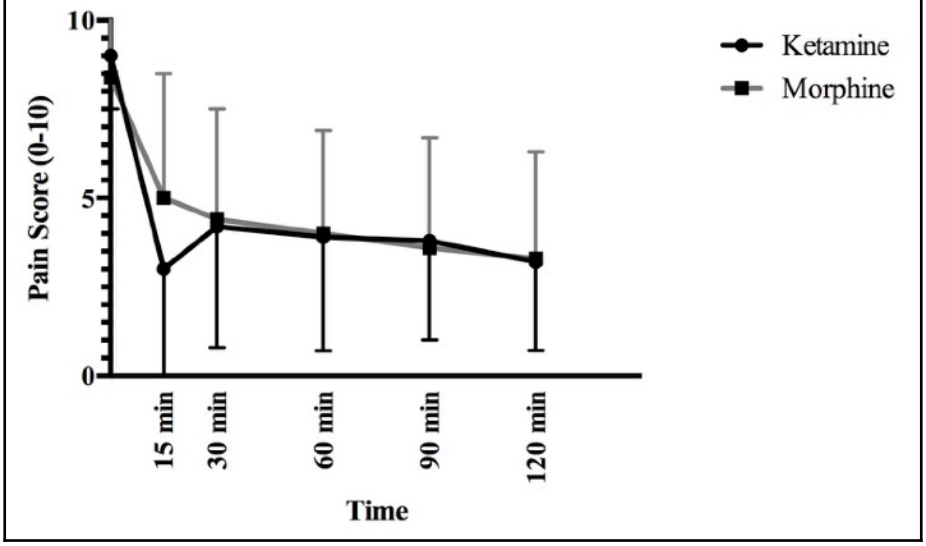
Background Geriatric patients presenting with acute pain pose a challenge to providers because of age-related changes in absorption, metabolism, clearance, and polypharmacy. Previous research suggests geriatric patients' acute pain is under treated in the emergency department. This has led many providers to consider administration of non-opioid analgesics for acute pain in geriatric patients.

Ketamine is an NMDA receptor antagonist that decreases pain via blockade of central sensitization, hyperalgesia, and wind-up in the spinal cord. Administration of subdissociative-dose ketamine, 0.1-0.3 mg/Kg, has demonstrated effective acute pain relief in non-geriatric patients with acute traumatic and nontraumatic pain either as a bolus or as a short infusion. An infusion over 15 minutes has been shown to decrease psychoperceptual side effects, nausea and vomiting, and dizziness. However, there have been no prospective trials evaluating the efficacy of subdissociative-dose ketamine administered as an infusion in geriatric patients presenting to the emergency department with acute pain complaints.

Methodology This was a prospective, double-blind, randomized controlled trial of patients aged 65 years or older experiencing moderate-to-severe acute abdominal, flank, cancer, or musculoskeletal pain >5 on 0-10 numeric rating scale. Investigators, nurses, and statisticians were blinded to group assignment. Patients were randomized to either ketamine 0.3 mg/Kg or 0.1 mg/Kg morphine diluted in 100 mL administered over 15 minutes. Fentanyl 0.5 µg/mL was administered for breakthrough pain. The primary outcome was a difference in pain scores at 30 minutes after infusion of the study medications. Secondary outcomes included the need for rescue analgesics at 30 or 60 minutes; pain scores at 15, 60, 90, and 120 minutes; and adverse effects. Adverse effects of study medications were evaluated with the Side Effect Rating Scale for Dissociative Anesthetics (SERSDA) and the Richmond Agitation Sedation Scale (RASS). Statistical analysis and sample size calculations were appropriate.

Result There were 60 patients enrolled in the study, with 59 completing the study (ketamine group N = 29 vs. morphine group N = 30). No significant differences were found in baseline patient

Figure 1. Pain Scores



characteristics. Mean age was 77 years, 23% were male, and mean baseline pain scores were approximately 9 on a scale of 0-10. Abdominal pain was the most common source of pain in both the ketamine and morphine groups (47% vs. 33%, P = NS), followed by fracture (17% vs. 23%, P = NS). Cancer pain rates were higher in the ketamine group (16.7% vs. 2.2%, P = NS).

There was no significant difference in pain scores at 30 minutes between the ketamine and morphine groups (Figure 1). However, the rate of full resolution of pain was significantly higher in the ketamine group at 15 minutes (52% vs. 17%, P < 0.05). Likewise, the ketamine group had a higher percent of patients whose pain scores were reduced to 3 at 15 minutes after administration compared to the morphine group (73% vs. 53%, P < 0.05). No significant differences were found in the need for rescue analgesia at any time point, or in any other outcomes at 30, 60, 90, or 120 minutes.

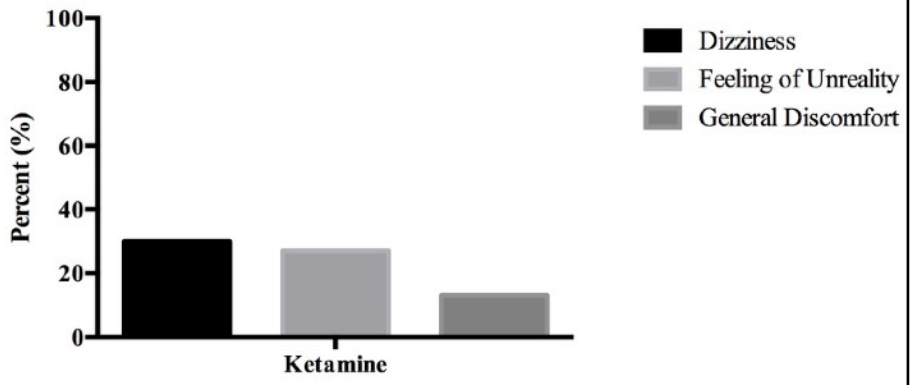
The rate of adverse effects was higher in the ketamine group at 15 minutes (87% vs. 47%, P < 0.05) and 30 minutes (73% vs. 37%, P < 0.05) compared to the morphine group. The rate of dizziness was significantly higher at 15 min.(63% vs. 30%, P < 0.05) and 30 min. (53% vs. 23%, P < 0.05) in the ketamine group. Rates of adverse effects in the ketamine group peaked at 15 minutes (Figure 2). No differences in adverse effects between the ketamine and morphine groups were found at 60 min. or later. No differences

Table 1. Adverse Effects

Time point	Dizziness		Nausea		Fatigue	
	Ketamine	Morphine	Ketamine	Morphine	Ketamine	Morphine
15 min	63%*	30%	14%	3%	27%	17%
30 min	53%*	23%	7%	7%	13%	20%
60 min	35%	20%	21%	7%	17%	17%
90 min	20%	7%	13%	7%	7%	17%
120 min	18%	17%	11%	7%	11%	20%

Note: *P < 0.05

Figure 2. Dissociative Symptoms



were found in the rate of fatigue or nausea between the groups at any time point (Table 1). No serious adverse effects occurred in either group.

Conclusion Subdissociative-dose ketamine administered – 0.3 mg/Kg over 15 minutes – resulted in similar analgesic efficacy but with much faster onset compared to morphine 0.1 mg/Kg for treatment of acute pain in the emergency department geriatric population. However, psychoperceptual side effects were more common in patients who received ketamine, though for a relatively short period of time.

Comment

Subdissociative-dose ketamine is becoming a popular alternative to opioids for the treatment of acute pain in the Emergency Department. At my small overseas critical-access hospital my emergency department colleagues have found subdissociative-dose ketamine to be efficacious with minimal side effects in the treatment of acute pain. This has allowed them to reduce the frequency of opioid administration. This is especially important given the opioid epidemic. With proper training and a written protocol we were able to expand this practice to our multiservice ward so our nurses could administer a subdissociative-dose ketamine infusion over 15 minutes for acute pain. This has decreased the number of times the anesthesia provider gets called in to manage acute pain. I would encourage anesthesia providers at other institutions to consider developing a subdissociative-dose ketamine protocol. You may find similar benefits.

Dennis Spence, PhD, CRNA

NOTES:

The **SERSDA scale** includes fatigue, dizziness, nausea, headache, feeling of unreality, changes in hearing, mood change, general discomfort, and hallucinations on a five-point scale, with "0" representing absence of adverse effects to "4" representing severe side effects.

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Pharmacology

Dexamethasone does not inhibit sugammadex reversal after rocuronium-induced neuromuscular block

Anesth Analg 2016;122:1826-30
DOI: 10.1213/ANE.0000000000001294
Buonanno P, Laiola A, Palumbo C, Spinelli G, Servillo G, Di Minno RM, Cafiero T, Di lorio C

Abstract

Purpose The purpose of this research was to explore whether or not dexamethasone, administered during general anesthesia for the prevention of PONV, affected the ability of sugammadex to reverse rocuronium.

Background Sugammadex was approved by the Food and Drug Administration in late 2015. It's mechanism of action is to encapsulate the steroidal neuromuscular blocking agents rocuronium and vecuronium, thereby rendering them unable to interact with receptors at the neuromuscular junction. This encapsulation and strong binding allows for the rapid restoration of skeletal muscle function. The steroidal non-depolarizing muscle relaxants rocuronium and vecuronium have a cyclopentanoperhydrophenanthrene structure. It is their structure that allows encapsulation by sugammadex. *In vitro* interactions between sugammadex and over 300 other molecules were tested; only three compounds appear to have an affinity for the cyclodextrin significant enough to break the bond between sugammadex and rocuronium or vecuronium: toremifene (an oral selective estrogen receptor modulator), fusicid acid (a topical antibiotic cream), and flucloxacillin (a penicillin). Dexamethasone also has a cyclopentanoperhydrophenanthrene structure as well as molecular dimensions that are very much like rocuronium.

In 2014, a published *in vitro* study reported that the efficacy of sugammadex may be diminished in the presence of dexamethasone. Dexamethasone has molecular properties similar to the steroid-based rocuronium molecule. *In vitro* using innervated primary human muscle cells, dexamethasone inhibited sugammadex's ability to encapsulate the rocuronium molecule.

Methodology This was a retrospective case-controlled review. The anesthesia records of ASA I or II patients who had elective surgery with general anesthesia that included rocuronium, sugammadex, ondansetron, or dexamethasone; aged 18 years to 65 years; with BMIs between 18 and 30 kg/m^2; and with 2 or more risk factors for PONV were analyzed. A total of 813 records were reviewed, but after applying appropriate exclusion criteria 45 records were placed into three mutually exclusive groups:

- **Control Group** - ondansetron immediately following anesthesia induction
- **Dexamethasone Early** - 8 mg immediately following anesthesia induction
- **Dexamethasone Late** - 8 mg just prior to reversal with sugammadex

General anesthesia was standardized, as was the timing of sugammadex administration and the use of acceleromyography for neuromuscular monitoring. The primary outcome variable measured across all three groups included the recovery time to a TOF ratio >0.9 to identify if delayed recovery could be associated with dexamethasone. Additionally, demographic data was extracted to identify confounding variables that may have influenced the results.

Result Demographic and clinical data were no different between the three groups. Recovery times, in seconds using an acceleromygraphy to calculate the quantitative train-of-four ratio, were not significantly different between groups. When sugammadex was administered to antagonize rocuronium blockade, dexamethasone 8 mg IV, given immediately following induction or just prior to administration of sugammadex, did not influence neuromuscular recovery times compared to the control group.

Conclusion The outcome of this small retrospective study did not support the previous results of an *in vitro* study that suggested dexamethasone used to prevent PONV would impair reversal of rocuronium by sugammadex. These results may not be generalizable to a larger population due to the fact that study patients had only moderate neuromuscular block prior to sugammadex administration.

Comment

As with any new drug that we use, we must become intimately familiar with its entire profile including possible drug interactions. While sugammadex has been approved for use in Europe for several years and a plethora of research has been published, use in the USA is limited by comparison. Our own clinical involvement is on the up-slope of the learning curve. I also appreciate the explanations offered by the authors regarding the differences in outcomes based on experimental technique, i.e. whether *in vitro* or *in vivo*, and how these differences guide us in interpreting results. However, I do agree that conflicting evidence, irrespective of experimental technique, warrants further investigation, and therefore I found this publication extremely useful as I anticipate widespread use of sugammadex. We must understand the clinical relevance of all studies. We certainly are not going to stop treating PONV with dexamethasone since the evidence supports its efficacy, so the probability of using the two drugs during the same anesthetic is high. Now that we have sugammadex available for clinical use we owe it to our patients to understand the drug and its complete profile. I do believe we are going to see massive improvements in outcomes because of sugammadex use; the complications related to neuromuscular blockade use will be problems of the past.

Mary Golinski, PhD, CRNA

Pharmacology

Ketamine-based anesthesia improves electroconvulsive therapy outcomes: a randomized-controlled study

Can J Anesth 2018;65:636–646
DOI: 10.1007/s12630-018-1088-0
Gamble JJ, Bi H, Bowen R, Weisgerber G, Sanjanwala R, Prasad R, Balbuena L

Abstract

Purpose The purpose of this study was to test the hypothesis that ketamine anesthesia was associated with antidepressant outcomes following Electroconvulsive Therapy (ECT) that were superior to ECT with propofol anesthesia.

Background Depression is a common psychiatric diagnosis and is often treated with oral antidepressants. When major depression persists despite pharmacologic treatment, psychiatrists may employ Electroconvulsive Therapy (ECT). ECT often produces rapid antidepressant effects. Side effects of ECT include cognitive changes, impaired memory, and relapse. Ketamine has been shown to produce rapid improvement in depression. Studies of a single IV infusion of ketamine have resulted in significant and almost immediate antidepressant effects in patients with both unipolar and bipolar depression. Repeat ketamine administration for two to four weeks has resulted in a marked decrease in depression for weeks after ketamine administration was ended. At least one study has suggested that ketamine without ECT compares favorably to ECT with sodium pentothal anesthesia. Lastly, ketamine may help reduce suicidal thoughts that sometimes occur early in the administration of oral antidepressant medications.

Methodology This was a randomized, double blind comparison of ketamine vs. propofol for ECT anesthesia. The ketamine group received ketamine 0.75 mg/Kg. The propofol group received propofol 1 mg/Kg. Both groups also received remifentanil 1 µg/Kg and succinylcholine 0.75 mg/Kg. The ketamine was mixed with Intralipid to look like propofol and the disguised ketamine and propofol was randomized for use in the study by the pharmacist. The patient, anesthesia provider, psychiatrist, nurses, and research assistant were each blinded to the patients study group.

Adult patients scheduled for ECT were eligible for the study. Patients were excluded if they were ASA physical status IV or V, had untreated hypertension or other major comorbidities or were pregnant. Outcomes were assessed in two categories: Remission and Response. Remission was defined as a reduction in the MADRS score (Montgomery–Åsberg Depression Rating Scale) to levels indicating no more than mild depression (≤ 10). Response was a 50% reduction in depression score. As a result, the study examined the number of ECT treatments needed to achieve Response and Remission.

Result The study was ended early following a planned interim analysis; only 27 subjects were

studied, 14 ketamine patients and 13 propofol patients. Demographics were similar between groups.

The time from induction of anesthesia for ECT to meeting discharge criteria was no different between groups, about 63 minutes. The rates of adverse events were also similar between groups. There was no statistical difference between groups in the rates of hypertension, hypotension, emergence agitation, or PONV. No patient in either group experienced hallucinations.

All ketamine patients achieved a Response vs. 83% of propofol patients. Ketamine patients achieved a Response with a median of 2 ECT treatments vs. 4 ECT treatments in the propofol group (P=0.01). All ketamine patients achieved Remission vs. 58% of propofol patients. Ketamine patients achieved Remission with a median of 3 ECT treatments vs. 7 ECT treatments in the propofol group (P=0.01).

Conclusion Compared to a propofol induction for ECT, ketamine was associated with a faster improvement in symptoms of depression, required fewer ECT treatments to achieve improvement, and had an identical 30-day remission rate. Ketamine anesthesia for ECT may reduce the number of ECT treatments needed for remission of treatment resistant depression.

Comment

Because we don't know why ECT treatments reduce major depression we have to pay attention when we find something that makes ECT more effective. For years now, the psychiatrists have been studying ketamine's effect on depression. Now we have some tentative evidence that using ketamine and ECT together may produce added benefit.

This study was planned to be "small" and include only 56 patients. For reasons that are unclear the investigators planned an interim external review of the results at 20 patients. Somehow that resulted in the study being ended at 27 patients because the external reviewers believed the results were so lopsided in favor of ketamine that it was unethical to continue the study knowing that some patients were going to be randomized to a less effective treatment. My point is this. It is unusual for a study to show such profound clinical significance, ketamine patients needed half as many ECT treatments, *and* statistical significance, with such a small sample size. This is one of the rare studies where one should pay less attention to how small it was and more attention to how big the results were.

Now we know psychiatrists often express a preference for induction drugs for ECT for fears that the seizure may not be long enough to produce therapeutic results with some induction drugs. So it's not like anesthesia is going to "help out" and do ECTs with ketamine and keep it to ourselves. But, you may want to share this study with the psychiatrists and make the offer to use ketamine. At the time I'm writing this ketamine is on the FDA shortage list and is not expected to be in normal supply until sometime in 2019, but that, as they say, is another problem.

Michael A. Fiedler, PhD, CRNA