STUDY PROPOSAL

Intraoperative Ketamine and Methadone for Laminectomy: Effect on Recovery, Postoperative Pain, and Opioid Requirements

IRB #: Pro00030109

NCT02252432

Date: 02/15/2020

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STUDY OBJECTIVES

1. To determine if intraoperative double NMDA antagonism with ketamine + methadone reduces postoperative pain scores and opioid consumption more than single NMDA antagonism with ketamine or methadone alone after lumbar laminectomy.
2. To compare the side effects and hospital course between post-laminectomy patients receiving intraoperative ketamine + methadone vs. ketamine or methadone alone.

BACKGROUND & SIGNIFICANCE

Post-laminectomy pain is associated with increased morbidity and postoperative complications (1). It not only prolongs the rehabilitation period, but also takes a financial and psychological toll on the patient. Despite hospital staff and resources being strained to keep these patients comfortable, management of back pain after laminectomy is often unsatisfactory. Baseline opioid requirements can be higher than the general population and often rise postoperatively. As a result, they are at higher risk of opioid side effects: respiratory and hemodynamic depression, non-obstructive ileus, nausea, vomiting, sedation, blurry vision (from miosis) and opioid induced hyperalgesia (2). Constipation and miosis are the only two side effects that patients do not develop tolerance to and thus, can worsen nausea and vomiting. To the primary medical team, it often becomes a game of trial and error to strike a fine balance between adequate pain control and side effects; especially staving off respiratory depression. Coanalgesics such as anticonvulsants and antidepressants have opiate-sparing effects and synergism with narcotics, but often take days to weeks before therapeutic gains are realized (3). Hepatotoxicity limits chronic use of antispasmodics that relieve back muscle spasms. NSAIDs are effective but post-surgical bleeding risks and potential gastrointestinal bleeding outweigh its benefits when there are safer alternatives. Although acetaminophen has a relatively benign side effect profile, its analgesic effect is poor on postoperative pain and is dose-limited by hepatotoxicity.

N-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine and methadone have been shown to have opioid sparing effects, minimize opioid tolerance and improve quality of postoperative pain control in chronic pain patients (4). The side effects and pharmacology of these two drugs are well known (5, 6). Ketamine and methadone both exhibit analgesic properties, the former having the additional benefit of maintaining respiratory drive and the latter being a long lasting opioid. Both medications are frequently used as the standard of care for perioperative pain management in patients undergoing spine surgery at our institution. However, this may vary at different institutions.

Ketamine, a phencyclidine derivative, has been in clinical use since 1958. It exerts its analgesic, amnestic and anesthetic effects on the brain and spinal cord by inhibiting presynaptic release of glutamate, an excitatory neurotransmitter, and non-competitively blocking calcium influx via NMDA receptor channels. Ketamine is also thought to activate mu and kappa opioid receptors (not reversible by naloxone) as well as blocking voltage-gated sodium channels like local anesthetics. Furthermore, ketamine has anticholinergic properties that promote bronchodilation (beneficial for asthmatics) and

tachycardia, which can be useful for hemodynamically unstable patients. The thalamo-neocortical and limbic systems are dissociated with ketamine i.e., the patient appears awake, with preserved pharyngeal and laryngeal reflexes, but is unresponsive and catatonic. Unlike narcotics, ketamine has the advantage of immediate, profound analgesia without life-threatening respiratory depression. Ketamine 125 – 250 µg/kg IV produces analgesia within 1-2 minutes, and has a duration of approximately five minutes (24).

Side effects (pupillary dilatation, nystagmus, dizziness, salivation, lacrimation, hallucinations) are dose-dependent and extremely rare in the analgesic dose range for ketamine. Doses to achieve analgesia with ketamine are much lower than that for anesthetic induction (2 to 10 mcg/kg/min IV vs. 1-3 mg/kg IV one time). In fact, most side effects are primarily reported with ketamine induction doses (19, 20). Even so, the drug was well tolerated and hallucination events were no different from placebo in a randomized, double-blind trial of intraoperative ketamine for spine surgery (7). Hallucinations and ketamine-induced cardiovascular stimulatory effects can be prevented by premedicating the patient with low-dose benzodiazepines (19, 20). Thus, with standard analgesic dosing and preemptive medications, ketamine side effects are virtually negligible.

The opioid-sparing effects and pain relief from ketamine have been well-documented. In a meta-analysis of 37 trials (>2000 patients) on perioperative ketamine use, post-surgical opiate requirements were less than placebo in the first 24 to 48 hours. In post spine surgery patients, there was a 30% reduction in morphine consumption over the first 48 hours after surgery, and a 25% visual analog scale (VAS) pain score reduction in the post-anesthesia care unit (8). Even at 6 weeks, postoperative pain scores and opiate consumption were significantly less in the ketamine group over placebo. For most prospective studies, ketamine was given as a single anesthetic induction dose with or without a low-dose infusion (9, 10). Although intraoperative ketamine is frequently used for postoperative pain at our institution, the evidence for use in spine surgery is sparse.

The other common analgesic with NMDA antagonism is methadone. Although it is used for opiate weaning to prevent withdrawal, its long elimination half-life (24-36 hours), low-abuse potential, and NMDA antagonism may be helpful in controlling pain in opiate-tolerant patients (16). Its potency is similar to morphine, though its duration of action can last 6-8 hours vs 3-4 hours with morphine. Since it is very hydrophobic, methadone has high oral bioavailability (80%) and easily crosses into the brain and fatty tissue, creating a depot that confers its long half-life. Methadone activates mu and delta opioid receptors. Like ketamine, it noncompetitively blocks NMDA receptor channels. Methadone time of onset is 8 minutes, which is similar to fentanyl and sufentanil. Doses > 20 mg will approximate methadone's elimination half-life. Liver metabolites, conjugated by CYP3A4 and CYP2D6, are inactive. Side effects are similar to other opioids e.g., nausea and vomiting, respiratory depression, etc., except less constipation and sedation than other opiates (17). These effects are dose dependent. The most potentially dangerous side effect of methadone is prolonged qT interval that can devolve into unstable arrhythmias and sudden cardiac death. It is recommended that patients receive an EKG prior to methadone administration, especially those who are hypokalemic and/or on drugs that prolong qT interval e.g., antipsychotics and drugs that inhibit CYP3A4/2D6 such as antifungals. Some studies demonstrated a weak but significant dose-dependent relationship with prolonged qT occurrence at doses 100-300 mg oral methadone (or at least 50 - 150 mg IV methadone) daily (18). A typical IV dose of

methadone for analgesia is 0.2 mg/kg, which amounts to 14 mg IV (14-28 mg oral form) in a 70-kg patient. This is well below reported threshold for prolonged qTc interval. Monoamine oxidase inhibitors should be used with caution as methadone can block monoamine uptake, e.g., serotonin, norepinephrine, precipitating serotonin syndrome and hypertensive crisis.

Patients given methadone during anesthetic induction demonstrated a 50% reduction in opiate requirements and VAS pain scores at 48h post spine surgery, but not at 24 hours (11). Several prospective, randomized controlled studies have found that methadone was superior to morphine in duration of postoperative pain relief and opioid requirements. The methadone group averaged 20.7 hours of sustained post-surgical pain relief compared to 6 hours with morphine and required significantly less quantities (11.5 $\pm$ 8.5 mg vs. 41 $\pm$ 14.1 mg) (11). Similar studies have confirmed methadone's benefits (12, 13). Thus, ketamine may have maximum benefit in controlling postoperative pain and decreasing opioid-induced side effects the initial 24 hours while methadone can continue to provide pain relief for up to 48 hours. The use of methadone in perioperative pain management is frequently employed by anesthesiologists caring for patients undergoing spine surgery at our institution and is within the standard of care.

Although it is clear that ketamine and methadone both provide significant post-op pain relief and opiate-sparing effects for chronic pain patients, their combined effects remain largely unknown. We hypothesize that post-laminectomy patients who were administered intraoperative ketamine and methadone will have improved postoperative pain scores than those receiving intraoperative ketamine or methadone alone. As explained above, methadone, an opioid agonist weak NMDA antagonist, and ketamine, a strong NMDA antagonist, are individually effective for pain control via separate molecular pathways. We believe that the treatment of pain by two separate pathways will cause a synergistic effect greater than the pain control produced by either medication alone. Our secondary hypothesis is that following lumbar laminectomy, patients given intraoperative ketamine and methadone will require less opiates postoperatively than those receiving ketamine or methadone only.

SUMMARY OF STUDY DESIGN

The proposed study is a randomized, double-blinded, placebo-controlled evaluation of intraoperative ketamine and methadone on postoperative pain and opioid requirements for chronic pain patients undergoing lumbar laminectomy.

Three intervention groups will include:

1. Ketamine group: A bolus of intravenous (IV) ketamine during induction (0.5mg/kg), and an IV infusion of ketamine intraoperatively (5 mcg/kg/min)
2. Methadone group: Will receive a single dose of IV methadone (0.2 mg/kg) preinduction.
3. Ketamine + methadone group: Will receive methadone (0.2 mg/kg) preinduction, a bolus of IV ketamine (0.5 mg/kg) during induction and and IV ketamine infusion intraoperatively (5 mcg/kg/min)

Perioperative anesthetic management will be standardized as well as post-anesthesia care unit (PACU) IV opioid administration, which will be based on verbal-rating scale (VRS) pain scores. Patients will be discharged from the PACU and sent to the floor. They will be placed on a pain medication regimen that often includes oral and IV narcotics as needed (PRN). Opiate consumption, VRS pain scores, and adverse events will be recorded on post-operative days one to three and at six weeks.

METHODS

I. Recruitment
    a. Study investigators will contact surgeons who routinely perform lumbar spine surgery and present the study protocol to the surgeons. During the preoperative visit (3 to 15 days prior to surgery), the surgeons and/or assistants will hand the study material packet to potential subjects. Those interested in participating will sign the initial patient contact letter, which includes their phone number and e-mail address.
    b. Study investigators will call these patients, explain the study protocol including the potential risks, benefits, and alternatives and address any questions/concerns. In this manner, potential subjects will have more than 24 hours to decide on signing the consent document.
    c. Only patients providing written consent and indicated that they have been introduced to the study prior to meeting with the anesthesiologists on the day of surgery will be able to participate and undergo screening.
    d. Screening procedures (see inclusion and exclusion criteria section) will ensure subjects meet all inclusion criteria. They will be subsequently randomized to one of three study groups according to a computer-generated randomization number table.

II. Study Medication Administration Protocol

    Unblinded M.D. investigators, whowill not be involved in data collection or managing the case, will be in charge of preparing the study drugs. After consent is obtained, the recruiter will give said unblinded investigator the subject's name, subject number, weight (in kg), height (in inches), and a sealed envelope containing the subject's group assignment and instructions for drawing up the study drugs. From this information, the unblinded investigator will prepare the study medications. Both ketamine and methadone are within the standard of care and are routinely used in anesthetic care at our institution. These medications are available in all CSMC post-anesthetic care units (PACU) as multi-dose vials, and are stored in a locked cabinet only accessible to PACU nurses not involved in the study. These nurses will give the required amount of study drugs requested by the unblinded investigator. The M.D. investigator will record the amounts given to each subject on a private record sheet that is only accessible to said investigator. There will be three syringes: one for ketamine, methadone and a syringe for IV infusion. The sham fluid will be 0.9% normal saline. Dosing will be based on mg/kg for IV bolus and mg/kg/h for IV infusion. An equal volume of the sham will be given. Anesthesiologist, patient and the investigator collecting the data will not be aware of the contents of the study syringe (double blind design). Each syringe will be labeled by increasing numbers following the sequence of

administration i.e., syringe #1 will be given pre-induction, syringe #2 will be given during induction, and syringe #3 will be infused over the duration of the surgery. To prevent accidental administration of 3 placebos, all syringes will have an additional random 4 letter label: those containing any vowel (A, E, I, O, U) at the end of the 4 letter combination will be designated as placebo syringes. The unblinded investigator will double check that no more than 2 syringes have this letter combination prior to handing off the syringes to the anesthesiologist. Once this has been verified, he will place a sticker over the alphabetic code to further blind the recruiter in case the placebo blinding procedure has been discovered. In the extremely rare event that the patient accidentally receives 3 placebos (no study drug), there is a rescue medication algorithm that calls for administering IV fentanyl boluses or increasing anesthetic depth to control pain. Date, IRB number, and subject number will be the only other labeling allowed on these syringes. Only the aforementioned unblinded M.D. investigators will know the syringe identities. However, the anesthesiologist can always be unblinded for emergencies that require identification of the study drug to direct appropriate treatment e.g., undocumented allergic reaction to the study medication, unexplained hemodynamic instability, unexplained altered mental status, etc. The unblinded investigator will meet with the anesthesiologist after the case is finished to report the amount of study drug given for pharmacy and billing purposes. The data collector, recruiter, surgeon, and nurses involved with the subject's care will not be allowed to review the anesthetic record unless given permission by the P.I. Only after the subject's completion of the study shall they have access.

Group	Study Medication (note - dose based on ideal body weight (IBW) in kg)
Ketamine	Preinduction: Sham methadone (0.9% normal saline IV bolus, volume (mL) equal to calculated methadone dose of 0.2 mg/kg) Induction: ketamine 0.5 mg/kg IV bolus Infusion: ketamine 5 mcg/kg/min IV
Methadone	Preinduction: 0.2 mg/kg methadone IV bolus Induction: Sham ketamine (0.9% normal saline IV bolus, volume (mL) equal to calculated ketamine induction dose of 0.5 mg/kg) Infusion: Sham ketamine (0.9% normal saline IV, rate equal ketamine infusion rate of 5 mcg/kg/min)
Ketamine + Methadone	Preinduction: 0.2 mg/kg methadone IV bolus Induction: ketamine 0.5 mg/kg IV bolus Infusion: ketamine 5 mcg/kg/min IV

III. Preoperative Evaluation (on the day of surgery):

a. In the preoperative holding area, patients will provide a detailed medical history, including demographic information (e.g., age, weight, height, ethnic origin, smoking history, anesthetic complications such as postoperative nausea and vomiting, baseline VRS pain scores, and current pain medication regimen. An anesthesiologist will perform

the physical exam and written informed consent will be obtained by one of the investigators.

b. Enrollment numbers: A total of 114 patients, aged 18-80 years, American Society of Anesthesiology (ASA) physical status I – III undergoing lumbar laminectomy will be randomly assigned to one of three study groups:

Group I	Ketamine (n = 38)
Group II	Methadone (n = 38)
Group III	Ketamine & Methadone (n= 38)

IV. Intraoperative period:

a. Premedication: Midazolam 20 ug/kg IV for anxiolysis, amnesia, and sedation synergism.

b. Standard monitors: automatic blood pressure cuff, non-invasive blood pressure three-lead electrocardiogram, capnograph, pulse oximeter, urinary temperature monitor and bispectral index (BIS) monitor will be used. Patient will be pre-oxygenated with a simple face mask at 6 L/min for at least 2 minutes.

c. Anesthesia induction technique: Fentanyl 50-100 mcg IV, propofol 1.5-3 mg/kg IV with lidocaine 1-1.5 mg/kg IV will be given for induction. Choice of muscle relaxant for intubation will be left up to the discretion of the anesthesiologist. Both histamine release from succinylcholine and the mild vagal blockade of rocuronium are negligible and are not known to interfere with pain control.

d. Normothermia will be maintained with forced-air warming and IV fluid warmers.

e. Administration of study medication will occur as follows:

Group	Dosing (IBW used for mg/kg dosing)
I – Ketamine	Preinduction: Sham (0.9% normal saline, volume calculated to match methadone dose) Induction: 0.5 mg/kg IV bolus Infusion: 5 mcg/kg/min IV
II – Methadone	Preinduction: 0.2 mg/kg IV bolus Induction: Sham (0.9% normal saline, volume calculated to match ketamine induction dose) Infusion: Sham (0.9% normal saline at infusion rate calculated and adjusted for weight to match ketamine bolus-infusion rate)
III – Ketamine & Methadone	Preinduction: methadone 0.2 mg/kg IV bolus Induction: ketamine 0.5 mg/kg IV bolus Infusion: ketamine 5 mcg/kg/min until surgery finish

f. Balanced anesthetic technique will be accomplished with desflurane and a propofol infusion. Desflurane 3-6% will be administered in 50% oxygen/50% air at a total fresh gas flow rate of 1-2 L/min. Propofol infusion will begin at 50-100 mcg/kg/min rate. Both desflurane and propofol rates may be titrated to keep BIS scores between 40 – 50 while maintaining heart rate and blood pressure within 25% of patient's baseline measurements. The anesthesiologist will have their choice of maintenance muscle

relaxant only stocked in our anesthesia carts (cisatracurium, succinylcholine, rocuronium, and vecuronium). Patients in the ketamine and ketamine & methadone group will be maintained on a ketamine infusion until the end of surgery. Similarly, those in the methadone alone group will receive a 0.9% normal saline infusion at an equivalent rate. This will be set by the investigators on a separate infusion pump prior to induction. The anesthesiologist will not be allowed to make any changes to this pump. Maintenance IV fluids will manage by the anesthesiologist. Neostigmine 2-5 mg IV and glycopyrrolate 0.2-1.0 mg IV will be used to reverse muscle relaxants. Patients will receive Ondansetron 4 mg IV before the end of surgery for antiemetic prophylaxis.

V. Rescue Medications Algorithm:

Intraoperative hemodynamic management for clinical studies involving infusions of ketamine: If heart rate or MAP values are more than 20% above or below the preoperative baseline values, hypovolemia and acute blood loss have been treated with crystalloids, colloids and/or blood transfusion, the treatment algorithm summarized below will be instituted:

	Step	Hypotensive	Normotensive	Hypertensive
Bradycardia	1	Desflurane decrease by 50% (to a minimum of 2%)	Glycoppyrolate 0.2 mg or/and atropine 0.4 mg	Desflurane increase 50% (max. 8%)
	2	If persist give atropine, decrease propofol infusion by 50%	If persist: reduce infusion of study drug by 50%	If persist: hydralazine 5 mg (max. 20 mg)
	3	If persist: ephedrine 5 mg (max. 20 mg) and reduce infusion of study drug by 50%	If persist: reduce infusion of study drug by 50%	If persist: hydralazine 5 mg (max. 20 mg)
Normal heart rate 50-100 bpm	1	Desflurane decrease by 50% to a min. of 2%	Do nothing	Desflurane increase by 50% (max. 8%)
	2	If persist: phenylephrine 100 mcg (max. 300 mcg)		If persist: labetalol 5 mg (max. 15 mg)
	3	If persist: reduce infusion of study drug by 50%		If needed, hydralazine 5 mg (max. 20 mg)
Tachycardia > 100 bpm	1	Desflurane decrease by 50% to a min. of 2%	Desflurane increase by 50% to a max. of 8%	Desflurane increase by 50% to a max. of 8%
	2	If persists: phenylephrine 100 mcg (max 300 mcg)	If persists: labetalol 5 mg (max 15 mg)	If persists: labetalol 5 mg (max. 15 mg)
	3	If persists: reduce infusion of study drug by 50%	If persists: give fentanyl 50 mcg boluses	If persists: give fentanyl 50 mcg boluses

Minimum mean arterial blood pressure = 55 mmHg

VI. Surgery Conclusion

Anesthetic and study drug infusion will be discontinued at skin closure. Patients will be extubated in the operating room and transferred to the PACU. VRS pain scores will be collected immediately upon arrival. The anesthesiologist will decide which postoperative pain medications to administer, but must use a standardized computer order set in CS-link. This set gives the option of using the following opiates: hydromorphone IV, fentanyl IV, or acetaminophen-hydrocodone PO. Ondansetron 4 mg IV will be given for nausea and vomiting. VRS pain scores will be measured again prior meeting PACU discharge criteria (awake and alert with stable vital signs and the absence of intractable side effects)

VII. Postoperative Period

a. After PACU discharge, pain control will be assumed by the primary surgical team or inpatient pain service. Pain medication regimens commonly include PRN dilaudid IV and oral narcotics e.g., percocet (oxycodone/acetaminophen) or norco (hydrocodone/acetaminophen). Thus, patients will always receive some form of narcotic as a part of their pain medication regimen.

PATIENT DATA COLLECTION

I. Preoperative demographics: age, weight, BMI, gender, ASA status, race, preoperative medications including beta-blockers and Lidoderm patches, prior back surgery, prior pain procedures, past medical/surgical history, social history (smoking, drinking, illicit drug use) allergies, history of postoperative nausea and vomiting, history of motion sickness and short-form 12 (SF-12) score after completing the survey. Name, phone number, e-mail address, and medical record number will collected and stored in a secured separate file to prevent bias and inadvertent unblinding. Only the study coordinator will have access to this file and the patient will be referred to solely by subject number.

II. Preoperative data: baseline VRS pain score, vital signs (blood pressure, heart rate, temperature, respiratory rate, oxygen saturation via pulse oximetry), 12-lead EKG interpretation, duration of pain, any abnormal lab results, additional surgical procedures (e.g., fusion, discectomy), and number of levels.

III. Intraoperative data:

- Vital signs (including blood pressure, heart rate), BIS values, every 5 – 10 minute intervals
- dosages of all medications given (anesthetics, analgesics, local anesthetics, rescue medications, adjuncts such as decadron, end-tidal desflurane concentration, rate of propofol infusion) , IV fluids, blood products, colloids, blood loss, urine output
- Duration of surgery (from skin incision to closure), duration of anesthesia (from IV induction until anesthetic drug discontinuation)

IV. Postoperative data:
- Time on arrival to PACU, departure, and total length of stay
- VRS pain score and nausea on arrival to the PACU, vital signs, opiate and antiemetic requirements in the PACU
- PACU complications such as respiration depression (respiratory rate < 8, need for naloxone, or respiratory arrest), hypoxemia or desaturation (SpO2 < 90% or need of supplemental oxygen to maintain SpO2 > 95%), hypotension, cardiac arrhythmias, myocardial infarction, nausea and vomiting, respiratory distress.
- Total opioid, adjuvant (e.g., anticonvulsants, antispasmodics, SSRI's) and antiemetic consumption at 24, 48, and 72 hours following surgery. If patients are discharged from the hospital prior to 72 hours, a telephone interview will be conducted to determine opioid/adjuvant consumption at home.
- VRS pain scores, vital signs and medication side effects (e.g., ketamine-induced hallucinations) at 24, 48, and 72 hours following surgery; time to return of daily activities (oral diet, return of bowel function, ambulation, showering) in days, any complications such as cardiac arrhythmias, global evaluation of anesthesia experience with 0 = worst, 10 = best
- Length of hospital stay

V. 6 week post-surgical assessment data:
- VRS pain score, opioid/adjuvant consumption, medication side effects (e.g., hallucinations, constipation, nausea and vomiting), SF-12 score.

Note: all opioid consumption will be converted to morphine equivalents for data analysis and presentation.

DATA ANALYSIS

Sample size estimates were based on the test for inequality of opioid consumption among the methadone, ketamine, and ketamine + methadone groups. We expect to observe at least a 30% decrease in opiate consumption between ketamine + methadone group and methadone or ketamine. Prior studies demonstrated that the postoperative opioid consumption and its standard deviation for methadone and ketamine are quite similar (10, 21). Mean opioid consumption was approximately 67 mg $\pm$ 38 mg (SD) for Menigaux's et al. ketamine group and median 63 mg (interquartile range, 27-86.1), which gives an estimated SD of 23. The expected group mean difference would be 18.9 for an approximate 30% decrease in opioid requirements. However, we would like to more conservative in our study since the aforementioned study populations were most likely skewed. For a two-tailed hypothesis with alpha 0.05, we would need at least 38 subjects per group to achieve a power of 0.8 to detect a 30% reduction in opioid consumption.

Two group t-test of equal means (equal n's)

	1	2	3	4
Test significance level, α	0.050	0.050	0.050	0.050
1 or 2 sided test?	2	2	2	2
Group 1 mean, μ_1				
Group 2 mean, μ_2				
Difference in means, $\mu_1 - \mu_2$	18.900	20.000	17.000	15.000
Common standard deviation, σ	23.000	23.000	23.000	23.000
Effect size, $\delta = \lvert\mu_1 - \mu_2\rvert / \sigma$	0.822	0.870	0.739	0.652
Power (%)	80	80	80	80
n per group	25	22	30	38

Similarly for VAS pain scores, previous studies found average scores to range from 2.8 $\pm$ 2.0 for methadone group and 5.4 $\pm$ 2.0 for the ketamine study (7, 10) . With alpha 0.05, power 0.8 and mean difference of 1.6, each group needs at least 17 subjects to observe a 30% reduction in VAS pain scores.

Two group t-test of equal means (equal n's)

	1	2	3	4
Test significance level, α	0.050	0.025	0.050	0.025
1 or 2 sided test?	2	2	2	2
Group 1 mean, μ_1				
Group 2 mean, μ_2				
Difference in means, $\mu_1 - \mu_2$	2.000	2.000	1.800	1.800
Common standard deviation, σ	2.000	2.000	2.000	2.000
Effect size, $\delta = \lvert\mu_1 - \mu_2\rvert / \sigma$	1.000	1.000	0.900	0.900
Power (%)	80	80	80	80
n per group	17	21	21	25

Based on the power analysis, a sample size of 38 patients for each group will sufficiently allow us to detect at least a 30% reduction in postoperative opioid consumption and VAS pain scores with 80% power using a two sample t-test, significance level of 0.05 (two-sided). Total sample size will be 114.

ANOVA will be used to compare the continuous variables among the three treatment groups, and when significant differences are determined, a Newman-Keuls multiple-comparison test will be used to determine intergroup differences. Continuous data not normally distributed are analyzed by Kruskal-Wallis test, and when a significant difference is found, a Mann-Whitney U test is used for post-hoc comparisons between the intergroups. Chi-squared test (or Fisher's exact test) is used to analyze the categorical variables such as side effects and sex distribution.

INCLUSION & EXCLUSION CRITERIA

I. Inclusion criteria:
    - 18 – 80 years old of either gender, scheduled for elective lumbar laminectomy

II. Exclusion criteria:
- ASA IV and above
- Intolerance, allergy, or contraindication to use of any medications used in this study
- Significant coronary artery disease (abnormal stress test, myocardial infarction within the last 3 months)
- Increased intraocular pressure (e.g., untreated glaucoma)
- Uncontrolled hypertension (BP > 140/90)
- Sleep apnea AND currently on continuous positive airway pressure (CPAP)
- Increased intracranial pressure or clinical signs thereof
- History of intracranial surgery, stroke, or brain aneurysm
- Cardiac arrhythmias particularly prolonged QT syndrome
- Drugs known to cause prolonged qT: class IA antiarrhythmics (quinidine, procainamide, dysopyramide), class III antiarrhythmics (sotalol, dofetalide, ibutalide, amiodarone), haloperidol, thioridazine, arsenic trioxide, HIV protease inhibitors, tricyclic antidepressants
- Individuals with significant psychological disorders including: schizophrenia, mania, bipolar disorder or psychosis
- Pregnant or lactating women
- Emergent laminectomy
- Those already receiving ketamine or methadone prior to surgery
- Morbid obesity (BMI > 40 kg/m^2) AND/OR weight $\geq$ 150 kg
- Chronic renal failure (creatinine > 2.0 mg/dL)
- Liver failure e.g., active cirrhosis
- Alcohol or substance abuse within in the past 3 months
- Uncorrected hypokalemia, hypomagnesemia, hypocalcemia (can be due to diuretics, mineralocorticoid use, laxatives)
- COPD/Hypercarbia
- Restrictive lung disease (pulmonary fibrosis, myasthenia gravis)
- Congestive heart failure
- Thyroid disease
- Organ transplant patients
- Drugs/substances known to inhibit methadone metabolism: macrolide antibiotics e.g., erythromycin, cimetidine, astemizole, voriconazole, grapefruit juice

DATA HANDLING/RESOURCING

Investigators will have access to the patients' medical records and the results of all examinations undertaken as part of this clinical trial. All data will be recorded in forms provided by the investigators. Collected data will be coded and used for research purposes only.

SUBJECT RECRUITMENT

Study investigators will contact surgeons and present this study protocol to them. Prior to surgery, (ideally during patients preoperative appointments) the surgeon will inform the patient of this study and obtain a consent for contact letter signed by the interested patient. The patient will also be provided with an informed consent form. Study staff will follow-up with the surgeon's office (or vice-versa) and conduct a phone interview with the patient to determine eligibility. Patients who intend on participating in the study will sign the informed consent form and the investigator will record that the subject has had completed their informed consent well before the scheduled procedure. Risk and benefits will be reviewed with the subject. They reserve the right to voluntarily exit the study at any time without any penalty. Patients will be explained that general anesthesia will be used during the study.

POTENTIAL RISKS

Ketamine has been approved by the FDA and is used widely in the U.S. for anesthetic and pain management arenas. It has been well-studied in both animal model and human subjects. Of note, the side effect likelihood listed below for ketamine represent the induction dose side effect profile. Ketamine side effects are dose-dependent, and subanesthetic ketamine doses such as that used for analgesia are mild and less likely to occur (6). For instance, CNS side effects (dizziness, dysphoria, confusion, drowsiness, hallucinations) analyzed from pooled data did not reveal any significant differences: 18% in postoperative ketamine plus morphine vs. 15% in morphine PCA groups (P = 0.31; RR, 1.27; 95% CI, 0.80, 2.01) (23). Incidence of CNS side effects for ketamine patients were 18%, 10%, 9%, and 0.7% with IV PCA, IV infusion, IV single dose, and epidural groups. The psychogenic effects (dysphoria, confusion, hallucinations) will be mitigated by midazolam premedication. Patients with significant coronary artery disease (abnormal stress test, recent angina, MI within the last 3 months) will be excluded due to increased cardiac demand (from increased blood pressure, tachycardia). Patients with increased intracranial pressure (ICP) and untreated high intraocular pressure (IOP) will also be excluded from the study.

	Very Likely (>25%)	Likely (10-25%)	Less Likely (1-9%)	Rare (<1%)
Ketamine	• Blurred vision • Confusion	• Increased or decreased blood pressure or heart rate • Mental or mood instability • Psychotic thoughts • Hallucinations	• Vomiting • Nausea • Nightmares • Drowsiness	• Difficulty talking • Irregular heart rhythms • Muscle tightness • Redness, or swelling at the injection site • Allergic reactions (rash, itching, difficulty breathing)
Methadone	• Drowsiness • Dizziness	• Low Blood Pressure	• Slower or faster heart	• Increased intracranial

		• Constipation • Nausea • Slowed respiratory rate	rate • Confusion • Orthostatic hypotension • Dry mouth • Biliary tract spasm • Blurred vision • Stomach cramps • Anxiety	pressure • Irregular heart rhythms e.g., prolonged qT which may devolve into Torsades de Pointes • Urinary retention • Heart failure • Pulmonary edema • Respiratory arrest • Hives/itching

Methadone carries the same side effect profile as other opiates (constipation, mild drowsiness, pruritus, nausea and vomiting, miosis, respiratory depression), with two chief exceptions - prolonged qTc interval and long-half life. Previous studies suggest that doses as low as 30 mg/day can prolong qTc interval > 0.5 seconds and those who developed Torsades de Pointes (TdP) had doses as low as 40 mg/day (25). 3.6% of subjects receiving methadone developed (TdP) and had abnormal baseline EKG. Erhet et al. also determined that low serum potassium levels, lower serum prothrombin levels (indicative of poor liver function and thus, drug metabolism), and concomitant use of drugs with higher CYP3A4 inhibition were positively associated with prolonged qTc. For our study, we are excluding patients who are morbidly obese, with liver disease, on medications known to inhibit CYP3A4 and/or have arrhythmias in their preoperative EKG.

Since methadone has a half-life of approximately 24-36 hours (22), respiratory depression risk may be increased when additional sedatives are given. Thus, we are excluding any high-risk patients who have poor respiratory status (COPD, any restrictive lung disease, sleep apnea). Nursing will be advised to avoid oversedation. If the patient goes into respiratory depression i.e., respiratory rate < 8 breaths per minute, naloxone (0.1-0.2 mg every 2-3 minutes to keep respiratory rate > 8) can be administered. Supplemental oxygen will be provided to maintain oxygen saturation > 95% during these episodes.

If the postoperative EKG demonstrates prolonged qTc interval of >470 ms for men and >480 ms for women OR a 60 millisecond (or 25%) increase from baseline, the patient will be placed on telemetry. Serum potassium and magnesium levels will be monitored closely and replaced as necessary. If the patient enters Torsades de Pointes and is hemodynamically unstable, prompt nonsynchronized electric defibrillation can be performed. A magnesium sulfate infusion will be started for treatment and prevention. If the patient does not respond to magnesium, transvenous overdrive pacing at 100 beats per minute will be instituted. Isopreterenol (starting at 2 mcg/min and titrating to heart rate of 100 beats per minute) can also be used as a temporizing measure while transvenous pacing is being setup.

The patient will be admitted to the critical care unit if they have hemodynamic instability, syncope, or ventricular ectopy, T wave alternans, AV block or QRS widening on their postoperative EKG.

In general, less likely and rare side effects are seen in higher than clinically acceptable doses or prolonged use of the drug. Those with co-existing diseases that increase the likelihood of the more rare and severe side effects such as increased intracranial pressure will be excluded. Ketamine has an elimination half-life of 3-5 hours while methadone's elimination half-life ranges from 24 – 36 hours (22). On average, lumbar laminectomy duration has been 2-3 hours. An additional 1-3 hours is spent in the PACU. Nausea and vomiting will be treated with an antinauseant such as ondansetron IV.

MANTAINANCE OF CONFIDENTIALITY

Patients' names will not be divulged and all data will be coded in the study records in accordance with standard HIPPA policy. Information gained during the course of the study will only be used by the investigators for the purpose of evaluating the effects of ketamine infusion with methadone during the intraoperative and postoperative period. All data will be coded in the study records. Copies of signed informed consent will be kept on file by the principal investigator, and no patient names or other identifying information will be used in any future publications.

SPECIAL PRECAUTIONS

All drugs will be used by an anesthesiologist who is familiar with them and trained to handle any untoward events related to medications

RISK-BENEFIT ASSESSMENT

Risks to subjects are minimal relative to the anticipated benefits (e.g., reduction in postoperative pain and opioid requirements, as well as reduction of opioid-associated side effects). Ketamine hallucinatory effects will be minimized with the use of benzodiazapines, namely Versed, and one-time methadone doses are well below toxicity levels, especially for prolonged QT syndrome. Analgesic doses of both drugs are well tolerated and side effects are transient. Chronic pain patients who are opiate-tolerant may benefit greatly from acute postoperative pain control using this novel drug combination. Thus, the low risk/benefit ratio clearly justifies this study.

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