Hackensack University Medical Center
Institutional Review Board

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Comparison of ketamine 0.1 mg/kg, 0.2 mg/kg, and 0.3 mg/kg intravenous doses for acute pain in the emergency department: A prospective, randomized, double-blind, active-controlled, clinical trial

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Table of Contents

I. Objectives of the Study

Primary Objectives

This study will prospectively compare the mean Numerical Rating Scale (NRS) pain score reduction amongst three recommended dosing strategies of intravenous ketamine (0.1 mg/kg, 0.2 mg/kg, and 0.3mg/kg) for acute pain in the emergency department (ED).

Secondary Objectives

This study will also examine the frequency of adverse events secondary to ketamine including fatigue, dizziness, nausea, headache, feeling of unreality, changes in hearing or vision, mood changes, generalized discomfort, and hallucinations, changes in vital signs. Subgroups for exploratory analysis based on the need for rescue analgesia within two hours of ketamine administration, adequate pain relief, previous opioid tolerance, and age (adults < 65 years old and > 65 years old).

II. Background Material

Pain is one of the most common reasons for presentation to the emergency department, with studies reporting it being responsible for up to 78% of visits. Accordingly, pain reduction is one of the primary goals of emergency medicine.[1] Opioids are among the most common analgesics used to treat pain in the emergency department.[2] The increasing use of opioids has made treating acute pain difficult due to increased concern for opioid tolerance, abuse, and misuse.[3]

The opioid epidemic in the United States is ongoing. From 1999 to 2016, a three-fold increase in opioid prescribing was reported by the Substance Abuse and Mental Health Services Administration.[4] Adverse effects secondary to opioids include respiratory depression, sedation, hypotension, and opioid abuse/misuse.[2] The Centers for Disease Control and Prevention (CDC) reported a two-fold increase in the rate of overdose deaths involving opioids from 2000 to 2014, with two-thirds of drug overdose deaths involving an opioid in 2014. Natural and semisynthetic opioids, including morphine, oxycodone, and hydrocodone, were four times more likely to be involved in overdose deaths than heroin and cocaine combined.[5]

In an effort to stop the rise of the US opioid epidemic, there has been an increased utilization of non-opioid pain medications in the emergency department. Ketamine has traditionally been used as a dissociative anesthetic agent with amnestic properties at doses of 0.5 – 4.5 mg/kg intravenous (IV). Ketamine is now considered a standard of care at low doses (0.1 – 0.3 mg/kg IV) as an opioid alternative for pain management in emergency departments across the United States.[6-8] Guidelines for the use of ketamine in acute pain within the emergency department have been approved by the Pharmacy and Therapeutics Committee and the Medical Executive Committee at Hackensack University Medical Center (Appendix B).

Current literature recommends a dose range of ketamine 0.1 – 0.3 mg/kg IV for pain, but no studies comparing doses within this range have been performed.[6-9] Available studies evaluate the use of ketamine against placebo, against morphine, as an adjunct to morphine, and as intravenous infusion versus bolus. This study will be the first to evaluate ketamine at doses of 0.1 mg/kg, 0.2 mg/kg, and 0.3 mg/kg IV to determine which correlates with the most efficacy and safety. While

these doses are already the standard of care for acute pain in the emergency department, we want to determine if any dose-related differences in pain score reduction or adverse effects exist.

Ketamine was studied as an adjunct to morphine in a trial designed to compare effectiveness with morphine alone. Sixty patients were split into three equal groups of morphine 0.1 mg/kg IV push alone (standard care), morphine 0.1 mg/kg IV push plus ketamine 0.15 mg/kg IV push, and morphine 0.1 mg/kg IV push plus ketamine 0.3 mg/kg IV push. Pain scores, need for rescue analgesia, changes in vital signs, and adverse events were collected and analyzed. The primary outcome was pain score reduction, with secondary outcomes measuring pain scores at each time point, patient-perceived analgesia, time and amount of rescue analgesia required, and global analgesic effectiveness. Adverse events were recorded and assessed at baseline and at each time point. The pain-intensity difference (PID) is a measurement of the baseline pain score minus the pain score at the specific time point. While PID was significantly different in the standard care group when compared with both ketamine groups at 30 minutes, it lost significance when compared to the ketamine 0.15mg/kg IV group at 60 and 120 minutes. There were no differences in analgesia between the two ketamine groups at any of the study endpoints. There were no differences in the use or amount of rescue analgesia between any of the groups, but the standard care group did require rescue analgesia sooner. While the study was not powered to detect a difference in the frequency of adverse events, no serious adverse events were noted. Dizziness was reported more in the ketamine 0.3 mg/kg IV group when compared with either group. The authors conclude that ketamine 0.3 mg/kg IV may be more efficacious than ketamine 0.15 mg/kg IV when used as an adjunct to morphine for acute pain in the emergency department.[10] This discrepancy in the analgesic effect of two recommended doses of ketamine warrants further investigation.

Motov and colleagues performed one of the first head to head studies of ketamine alone and morphine alone for pain in the emergency department in 2015. In this prospective, double-blind, single center trial, 90 participants were randomized to either ketamine 0.3 mg/kg IV push or morphine 0.1 mg/kg IV push. The primary outcome was a comparative reduction in pain scores at 30 minutes after medication administration, need for rescue analgesia, vital sign changes, and adverse effects also collected. All patients reported reductions in their pain scores at 15 and 30 minutes, with no statistically significant differences between the two groups. At the primary outcome of 30 minutes, the mean difference in pain score between the ketamine and morphine group was 0.2 (95% CI -1.19 to 1.46; $p = 0.97$). There was no significant difference in the need for rescue analgesia between the two groups until 120 minutes, where the ketamine group did require more rescue fentanyl (percentage difference 17%, 95% CI 1% to 34%). There were no serious adverse events in either group or clinical concerning changes in vital signs. No adverse events required treatment in either group. However, ketamine patients reported a statistically significant increase in the number of adverse events immediately after medication administration and at 15 minutes (percentage difference 38%, 95% CI 18% to 57%). The authors conclude that ketamine 0.3 mg/kg IV provides analgesic efficacy and safety comparable to morphine for acute pain in the emergency department.[11]

In order to investigate the analgesic effect and safety of ketamine in the geriatric population, Motov and colleagues performed a prospective, randomized, double-blind trial comparing ketamine to morphine. They enrolled sixty patients aged 65 and older and randomized them

equally to either ketamine 0.3 mg/kg IV infusion or morphine 0.1 mg/kg IV infusion. The primary outcome was a reduction of pain scores between groups at 30 minutes. Secondary outcomes included the need for rescue analgesia and adverse events. While the ketamine group had a significant reduction in pain scores at 15 minutes, scores were similar between the groups at the primary outcome of 30 minutes through the 120 minute end point. There was no difference in the need for rescue analgesia at 30 or 60 minutes, but the morphine group did require significantly more rescue analgesia at 120 minutes. The study demonstrates that ketamine administered at 0.3 mg/kg IV provides analgesic efficacy comparable to morphine IV for acute pain in geriatric emergency department patients. There was a statistically significant difference in adverse events in the ketamine group when compared with the morphine group at both 15 and 30 minutes (percentage difference 40%, 95% CI 18.4% to 61.6% and percentage difference 36.67%, 95% CI -13.26% to 60.7%, respectively). Dizziness, feeling of unreality, and general discomfort were reported more and with greater severity in the ketamine group at 15 minutes.[9] While the study was not powered to detect differences in adverse events between the groups, it does highlight the need to determine the most efficacious doses of ketamine with minimal adverse events.

The dose recommendation for intravenous ketamine for analgesia in the emergency department has been extrapolated from the current literature. In 2017, the American College of Emergency Physicians (ACEP) released a policy statement regarding sub-dissociative doses of ketamine for acute pain in the Emergency Department. The policy statement recommended ketamine be dosed at 0.1-0.3 mg/kg IV over 10-15 minutes and that further research was needed to better define the maximally effective and safe dose.[12] Likewise, the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists published a consensus guideline on the use of intravenous ketamine infusion for acute pain management in 2018. The recommendation in these guidelines was that ketamine dosing should not exceed 0.35 mg/kg IV bolus.[13] This recommendation was specifically for surgical patients and cannot be extrapolated to patients with acute pain in the Emergency Department. No recommendations on choosing appropriate dosing within this range was given.

A literature review was performed that searched for randomized clinical trials involving ketamine IV boluses for acute pain in the Emergency Department. Studies involving continuous infusions or intranasal routes of ketamine administration were not included. Thirteen randomized clinical trials were identified meeting this criteria.[9-11, 14-23] None of these trials directly compared ketamine doses within the 0.1-0.3 mg/kg range for pain score reduction and adverse events. Many of these trials concluded with the recommendation that further studies were needed to evaluate the optimal dosing of ketamine for acute pain and determine which populations are most ideal for its use. This study will be the first to evaluate ketamine for acute pain in the emergency department at standard of care doses (0.1 mg/kg, 0.2 mg/kg, and 0.3 mg/kg IV) to determine which dose correlates with the most efficacy and safety.

III. Drug Information

Ketamine is a dissociative anesthetic with amnestic properties that is used for analgesia at low doses. It works primarily through *N*-methyl-D-aspartate receptor antagonism, with a lesser degree of effect on nicotinic, opioid, muscarinic, and dopaminergic receptors. It has an onset of

action of 30 seconds with a variable duration for analgesic effect, ranging from 2-4 hours. Ketamine is primarily metabolized in the liver and eliminated by the kidneys. The half-life of ketamine is variable, with an average of 2.5 hours reported in the literature. Side effects associated with ketamine are fatigue, dizziness, nausea, headache, feelings of unreality, changes in hearing, changes in vision, mood change, generalized discomfort, and hallucination.[24]

IV. Inclusion Criteria

Patients will be included if they present to the Adult Emergency Department with (all of the following):

- Acute pain (including acute on chronic pain)
- Pain score of moderate to severe ($\geq$ 4/10) on the Numerical Rating Scale
- Provider determines the patient requires intravenous ketamine for analgesia

V. Exclusion Criteria

Patients will be excluded from the study based on our existing ketamine for acute pain management in the emergency department guideline at Hackensack University Medical Center (Appendix B).

- History of hypersensitivity to ketamine
- Altered mental status
- Psychiatric illness
- Known history of renal or hepatic insufficiency
- Acute head or eye injury
- Suspected intracranial hypertension or mass
- Headache as the chief complaint
- Alcohol or drug abuse
- Received an analgesic within the last four hours
- History of congestive heart failure
- History of aortic or brain aneurysm
- Active Chest Pain
- Porphyria
- Active methadone treatment
- Pregnant or breastfeeding
- Signs of respiratory, hemodynamic, or neurologic compromise
    - Systolic blood pressure < 90 mmHg or > 180 mmHg
    - Heart rate < 50 beats per minute or > 150 beats per minute
    - Respiratory rate < 10 breaths per minute or > 30 breaths per minute
    - Glasgow Coma Score < 15
- Previously received ketamine $\leq$ 0.3 mg/kg IV for acute pain in the emergency department

VI. Recruitment Procedures

This is a single-center, prospective, randomized, double-blind, active controlled trial that will identify patients in the emergency department with acute pain who meet the eligibility criteria from January 2019 through January 2021 to achieve a sample of at least 180 patients.

VII. Definitions

Adequate pain relief:

- A score decrease on the Numerical Rating Scale (NRS) by $\geq$ 3 points

Moderate pain:

- A NRS score of 4-7 out of 10 per hospital policy

Severe pain:

- A NRS score of 8-10 out of 10 per hospital policy

Rescue analgesia:

- Any IV analgesic to be determined by the treating provider

Opioid tolerant:[25]

- Patients receiving, for one week or longer, at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid

VIII. Methodology

This is a single-center, prospective, randomized, double-blind, active-controlled trial. Patients who meet inclusion criteria and none of the exclusion criteria will be enrolled from January 2019 to January 2021 to achieve a goal sample size of 180 patients. Data such as demographics, self-reported pain score, adverse drug events, vital signs, and need for rescue analgesia within two hours of ketamine administration will be reported. Outcomes will include pain score reduction, incidence and severity of adverse drug events, adequate pain relief, and need for rescue analgesia within two hours of ketamine administration. All data will be entered in a password protected data sheet for proper analysis. No patient identifying data will be recorded.

The administration of ketamine 0.1 – 0.3 mg/kg IV for acute pain in the Adult Emergency Department was approved at the September 2018 Pharmacy and Therapeutics Committee and is currently standard of care. Education was provided to all providers and nurses in the emergency department.

Patient screening, enrollment, and data collection will be performed by the treating resident or attending who will remain blinded. The Primary Investigator will also remain blinded and the ED pharmacists will be unblinded to facilitate ordering and delivery of the study drug.

Patients who consent to the study and meet eligibility criteria will be randomized to one of three doses of ketamine (0.1 mg/kg, 0.2 mg/kg, or 0.3 mg/kg) to be given IV infusion over 20 minutes. The block randomization list will be generated by the Hackensack Meridian Health Biostatistician prior to patient enrollment. Pharmacy investigators will maintain the randomization list and deliver the medication to the nurse in a blinded fashion. The medication will be prepared as a 0.1 mg/kg, 0.2 mg/kg, or 0.3 mg/kg dose in a 100 mL solution of dextrose 5% or sodium chloride 0.9% according to the predetermined randomization list. If there is a significant delay from the initial pain score to the study dose of ketamine administration, the patient will be withdrawn from the study and receive standard of care treatment. If pain is not controlled after the administration of ketamine, providers can order a rescue analgesic of their choice.

Patient history will be reviewed for known allergies, resuscitative equipment will be readily available, and the type and intensity of pain prior to administration will be documented. Baseline

vital signs, such as blood pressure, heart rate, and respiratory rate, will be assessed prior to IV administration of ketamine and at 120 minutes after infusion or upon discharge, whichever is sooner. The patient's self-reported pain score, need for rescue analgesia, and any adverse drug effects will be reassessed within 15 minutes from the end of the infusion and then every 30 minutes for up to 120 minutes or until discharge, whichever is sooner. Incidence, severity, and total number of adverse drug events will be documented using the Side Effects Rating Scale for Dissociative Anesthetics (SERSDA).

Procedure:

- Patient consent, screening, and enrollment will be performed by the treating resident or attending who will remain blinded
- Patient will be assigned a subject number
- Treating resident or attending will notify the ED pharmacist that a patient has been enrolled in the trial
- ED pharmacist will notify the IV room and place the study drug order
- Either the ED pharmacist or a pharmacy supervisor will randomize the subject based on the predetermined randomization list
- Study drug will be prepared as 0.1 mg/kg, 0.2 mg/kg, or 0.3 mg/kg IV dose in a 100 mL solution of dextrose 5% or sodium chloride 0.9%
- ED pharmacist will promptly deliver the study drug to the ED
- Baseline vital signs will be assessed prior to starting the study drug infusion
- Study drug will be administered via IV infusion over 20 minutes
- Treating resident or attending will reassess the patient at 15 minutes from the end of infusion, at 30 minutes from the end of infusion, and then every 30 minutes for up to 120 minutes or until discharge, whichever is sooner

IX. Statistical Considerations

Randomization

The study participants will be randomly assigned into one of the three dose groups in the ratios of 1:1:1. Block randomization will be used to balance the sample size in each group.

Primary Outcome

The primary outcome is the numerical rating scale (NRS) pain score reduction from baseline to 120 minutes after the injection. The null hypothesis is that there is no difference among those three doses with respect to the mean score reduction.

Describing Data

The continuous variables (such as age of participant at the time of study) will be summarized using mean, median, standard deviation, interquartile range, range, minimum and maximum. The discrete variables (such as sex) will be summarized using frequency and percentage.

Exploring Differences

The two-sample Student's t-test will be used to compare the continuous variables between groups. If the normality assumption is violated, the Wilcoxon rank sum test will be used. The Shapiro-Wilk test will be used to evaluate the normality. The one-way analysis of variance (ANOVA) will be used to compare the continuous variables among groups. The Bartlett test will be used to evaluate the homogeneity of variances. The Tukey Honest Significant Differences test will be used to perform the multiple comparisons. If the normality assumption or homogeneity of variances assumption is violated, the Kruskal-Wallis one-way ANOVA by ranks will be used. The Dunn test will be used to perform the multiple comparisons.

The chi-square test will be used to compare the categorical variables between or among groups. If the expected frequency in any cell of the contingency table is less than 5, the Fisher's exact test will be used.

The 95% confidence interval on the variables of interest will be calculated. The 2-sided p value will be reported for each test. A p value of 0.05 or less will be considered an indication of statistical significance.

Exploring Associations

When necessary, graphical techniques will be used to display the statistical results. The scatter plots will be used to explore the associations between two continuous variables, and the Pearson's correlation coefficient or Spearman's correlation coefficient will be calculated to assess the potential linear association between two continuous variables based on the normality of data. Due to the nature of exploratory study, the regression models will be explored if there is any significant difference identified from the results of previously described statistical testing.

Conducting Analysis

Statistical analysis will be performed using the R language (R Core Team [2018]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.) or SAS software, Version 9.4 for Windows (SAS Institute Inc., Cary NC, USA. URL http://www.SAS.com).

Power and Sample Size

There is no existing study from which the reductions in NRS score were compared among the three doses of interest. Therefore, this study is considered an exploratory study to explore the possible reduction in NRS score as well as the chance of developing adverse events under a randomized clinical trial setting. With the consideration of both efficacy and safety, we propose including 60 subjects in each group in order to get more information regarding the safety for planning on a larger scale study.

After finishing the exploratory study, based on the mean reduction in each group, if we can find the potential clinical benefits are important, we will then estimate the necessary sample size in order to show the statistical significance. For example, if we can find the potential of clinical importance in primary outcome (such as a mean difference of 1.25 between consecutive doses with the standard deviation of 3.4), in order to show that the reductions are different among doses, with the significant level of 0.05 and power of 80%, if we want to have equal number of

patient in each group, we will need to have 157 patients in each group. That is, a total of 471 patients (157 in each group) will be needed.

X. Discomfort and Risks
The risks of this study are minimal, as ketamine is currently the standard of care for acute pain in the Adult Emergency Department at Hackensack University Medical Center.

Side effects associated with ketamine are fatigue, dizziness, nausea, headache, feelings of unreality, changes in hearing, changes in vision, mood changes, generalized discomfort, and hallucinations.

Emergence reactions will be treated per hospital protocol with short active benzodiazepines. Midazolam 1 mg IV once (or 0.5 mg IV in the elderly) administered by the provider is typically sufficient, but doses may be repeated if necessary.

If there is a significant delay from the initial pain score to the study dose of ketamine, the patient will be withdrawn from the study and receive standard of care treatment. If pain is not controlled after the administration of ketamine, providers can order an IV analgesic of their choice as a rescue analgesic.

XI. Benefits
There will be no direct benefits to patients whose data is included in the analysis. The results of this study will help to better determine the ideal dose of intravenous ketamine for acute pain in the emergency department.

XII. Criteria for Evaluating Response
Specific patient information will be obtained from patients using a data collection form (Appendix A) and will include

- Demographics (age, sex, weight)
- Type of pain
- NRS pain rating
- Previous opioid usage
- Need for rescue analgesia
- Vital signs (heart rate, respiratory rate, blood pressure)
- Presence of side effects secondary to ketamine

XIII. Confidentiality
All study related materials will be kept confidential as required by law. Written documentation and computer files will remain in a locked or password protected location, with access given to those directly responsible for the conduct of the study. In addition, all information will be recorded in such a manner that subjects whose data is included in the analysis cannot be identified directly or through identifiers linked to the subjects. A data collection tool can be found at the end of this protocol (Appendix A).

XIV. Credentials, Training

All investigators have completed the Collaborative Institutional Training Initiative.

List of investigators

- Gabrielle Procopio, PharmD, BCPS
- Irene Yang, PharmD
- David Zodda, MD, FACEP
- Nicole Webb Barbash, DO
- Marie-Therese Estanbouli, PharmD
- Ilya Aleksandrovskiy, MD
- Danielle Tompkins, PharmD, BCCCP

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XVIII. Appendix A

Demographics				
Subject #:	**Date/Time:**		**Age:**	**Sex:** Male / Female
Opioid Tolerant?*: ☐ Yes ☐ No	**Weight (kg):**	**SBP:**	**HR:**	**RR:**
Initial Pain Score Immediately Prior to Randomization (0-10):				

***Opioid tolerant**: Patients receiving, for one week or longer, at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid

Eligibility

If the subject does not meet all of the eligibility criteria, do not proceed with randomization.

Inclusion Criteria (if any answer is "no", stop immediately):

1) Acute pain (including acute on chronic)?

Type of Pain (Circle)

- Abdominal
- Flank
- Back
- Musculoskeletal
- Complex Regional Pain Syndrome
- Neuropathic
- Radicular
- Sickle Cell
- Trauma
- Other _____

2) NRS pain score ≥ 4/10?

3) Provider determines the patient requires intravenous ketamine?

Exclusion Criteria (if any answer is "yes", stop immediately):

1) History of hypersensitivity to ketamine?
2) Altered mental status?
3) Pregnant or breastfeeding?
4) Psychiatric Illness?
5) Known history of renal or hepatic insufficiency?
6) Acute head or eye injury?
7) Suspected intracranial hypertension or mass?
8) Headache as the chief complaint?
9) Alcohol or drug abuse?
10) Received an analgesic within the last 4 hours?
11) History of congestive heart failure?
12) History of aortic or brain aneurysm?
13) Active chest pain?
14) History of porphyria?
15) Active methadone treatment?

16) Signs of respiratory, hemodynamic, or neurologic compromise?
Defined as SBP < 90 mmHg or > 180 mmHg, HR < 50 or > 150, RR < 10 or > 30, or GCS < 15.
17) Previously received ketamine ≤ 0.3 mg/kg IV for acute pain in the emergency department

I have reviewed all of the inclusion and exclusion criteria and the patient is a candidate for this study: ☐ Yes ☐ No

Treatment

Side Effects Rating Scale: 0 = No Change / 1 = Weak / 2 = Modest / 3 = Bothersome / 4 = Very Bothersome

	15 Minutes	30 Minutes	60 Minutes	90 Minutes	120 Minutes
Pain Score (0-10):					
	Side Effect Rating Scale Score (0 - 4)				
Fatigue					
Dizziness					
Nausea					
Headache					
Feeling of unreality					
Changes in hearing					
Changes in vision					
Mood changes					
Generalized discomfort					
Hallucination					
Rescue Analgesia Needed? (Y/N)					

Vital signs at 120 minutes or discharge	**SBP:**	**HR:**	**RR:**

_____
Name of Provider Collecting Data

_____
Signature of Provider Collecting Data

_____/_____

Date Time

XIX. Appendix B

Hackensack Meridian Health
Hackensack University Medical Center Campus
IV Medication Guidelines

IV SUBANESTHETIC KETAMINE FOR ACUTE PAIN MANAGEMENT IN THE ADULT EMERGENCY and TRAUMA CENTER (ETC)

SCOPE

- Patients under the care of the ETC may receive IV ketamine for the management of acute pain under the direct supervision of an attending physician
- Registered nurses in the ETC may administer IV ketamine for treatment of acute pain as an intermittent infusion in doses not to exceed those outlined in this guideline
- The use of IV ketamine for procedural sedation is outside of the scope of this guideline and is described elsewhere

INDICATIONS

- Ketamine can be used as single agent or as a part of a multi-modal pain regimen for the treatment of moderate or severe pain. Interest in ketamine has emerged as an alternative to opioid analgesics to reduce the overall exposure to opioids and potential for abuse.
- Sub-anesthetic doses of ketamine have demonstrated efficacy in the treatment of various pain types: abdominal, flank, back, musculoskeletal, complex regional pain syndrome, neuropathic and radicular pain, and sickle cell crisis

THERAPEUTIC CATEGORY

Anesthetic agent with analgesic properties

CLINICAL PHARMACOLOGY

Rapid acting anesthetic with analgesic properties associated with the endogenous release of catecholamines, which may elevate blood pressure and heart rate with minimal respiratory depression at analgesic doses.

MECHANISM OF ACTION

- Central and peripheral non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors
- Inhibits serotonin and dopamine reuptake and inhibits voltage-gated sodium and potassium channels

PHARMACOKINETICS

- Onset of action: 30 seconds
- Duration: Variable for analgesic effect (2-4 hours)
- Metabolism: Hepatic; metabolite: norketamine (25% activity of parent compound)
- Half-life: 2.5 hours

CONTRAINDICATIONS

- Hypersensitivity to ketamine
- SBP > 180 and DBP > 100 mmHg
- HR < 50 or > 150 bpm
- Elevated intracranial pressure
- Increased intraocular pressure
- Pregnant or breastfeeding
- Acute head or eye injury
- Congestive heart failure - stage III and IV (myocardial depressant effects)
- Aneurysm
- Angina
- Psychiatric disorders
- Porphyria
- Active methadone treatment

RELATIVE CONTRAINDICATIONS

- SBP <90 or > 140 mmHg
- Renal or hepatic insufficiency
- Alcohol or drug abuse
- Coronary artery disease

PRECAUTIONS

- Emergence reactions (vivid dreams, hallucinations, frank delirium, confusion, excitement, or irrational behavior) are dose-related but may occur at the subanesthetic doses used for treatment of acute pain
- Patients > 65 years old

DOSAGE AND ADMINISTRATION

1. Dosages:

- Single dose of 0.1 – 0.3 mg/kg/dose (maximum single dose: 30mg) administered over 20 minutes via intermittent infusion
    - Lower doses should be initiated for elderly patients or those with renal/hepatic dysfunction
    - Doses greater than 0.3 mg/kg/dose may lead to dissociative effects
- Dose may be repeated after 60 minutes up to a total cumulative dose of 0.3mg/kg or 30mg
- An additional dose may be repeated after 4 hours for patients requiring ongoing analgesia while remaining in the ED

2. Standard Dilution: Weight based dose diluted into 100 mL D_5W or NS

TREATMENT OF EMERGENCE REACTION

- Emergence reaction may be treated with short acting benzodiazepines
- Midazolam 1mg IV once (0.5mg IV in the elderly) administered by the provider is typically sufficient
    - Doses may be repeated if necessary

DRUG INTERACTIONS

Ketamine is a substrate for CYP2B6, CYP2C9, & CYP3A4. The following includes, but is not limited to a list of drugs that may increase the levels/effects of ketamine.

- Sertraline, paroxetine (2B6)
- Fluconazole, nicardipine, NSAIDs, sulfonamides (2C9)
- Azole antifungals, clarithromycin, propofol, nicardipine (3A4)

ADVERSE REACTIONS

- Hypertension
- Tachycardia/bradycardia
- Tonic/clonic movements, tremor
- Increased intracranial pressure
- Emergence reaction/ dissociative effects (vivid dreams, hallucinations, frank delirium, confusion, excitement, or irrational behavior)
- Visual disturbances (diplopia and nystagmus)
- Nausea, vomiting
- Skin rash
- Headache
- Fatigue

NURSING GUIDELINES & MONITORING

- Review patient history for known allergies
- Resuscitative equipment readily available
- Assess type and intensity of pain prior to administration and document using appropriate pain scale
- Monitoring requirements for patients receiving IV ketamine with each dose:
    - Baseline BP, HR, RR and pain assessment prior to IV administration
    - Reassess BP, HR, RR and pain assessment within 15 minutes from end of infusion
    - Reassess RR and pain assessment 30 minutes from end of infusion and then as per unit protocol
- Assess for confusion, delirium, and visual disturbances; implement safety precaution as needed

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