

Cover Page

TITLE: Ketamine versus Fentanyl for Surgical Abortions: A Randomized Controlled Noninferiority Trial

NCT NUMBER: 04871425

DOCUMENT DATE: 3/25/2021

PROJECT SUMMARY

Ketamine is commonly used for procedural sedation and analgesia. It is widely used for trauma cases in the emergency department and is considered a superior agent in the outpatient setting due to its lack of respiratory and cardiovascular depression. In chronic opioid users, ketamine decreases acute pain and reduces postoperative opioid consumption. Few studies have examined the use of ketamine for surgical abortions. Previous studies found significant rates of emergence phenomena; however, this can be prevented if a benzodiazepine is given at the same time. Ketamine deserves further study to determine whether it is an acceptable alternative to a standard opioid-based regimen for surgical abortion. Our primary objective is to compare patient satisfaction after surgical abortion among patients receiving IV ketamine versus IV fentanyl for procedural sedation. Our secondary objectives include postoperative pain,

additional pain medication used, and postoperative opioid use after the procedure. Our hypothesis is that ketamine will provide similar patient satisfaction and reduce postoperative opioid use. This will be a randomized controlled noninferiority clinical trial of 84 women receiving either IV ketamine with IV midazolam or IV fentanyl with IV midazolam for outpatient one day surgical abortions up to 13, 6/7 weeks gestation. Both groups will receive a standardized paracervical block and additional pain medication as needed. Our study has the potential to introduce IV ketamine as a satisfactory medication for outpatient surgical abortions. Ketamine may decrease the need for IV fentanyl, reduce postoperative opioid use, and may prove to be a superior analgesic for chronic opioid users.

PROPOSAL NARRATIVE

Background

First-trimester surgical abortions are one of the most common outpatient procedures worldwide. Approximately 46 million are performed annually, with over 600,000 occurring in the United States.¹ Although it is a quick procedure, 78%–97% of patients still report at least moderate pain.¹ Many different techniques have been used for pain control during this procedure. From most common to least common, providers use the paracervical block (PCB), oral anxiolytics, moderate sedation or general anesthesia, and newer research has found promise in auricular acupuncture.^{2,3} Most providers use intravenous moderate sedation (38%) or the PCB with an oral medication (33%).² In a recent survey, most clinics who use local anesthesia supplement with IV fentanyl in doses of 50-100 mcg. A recent trial comparing IV fentanyl to placebo found a 1-point difference in pain on an 11-point scale. However, the authors question the benefit of this reduction in pain in light of fentanyl's various side effects including dizziness and drowsiness, the requirement for additional monitoring and resuscitative equipment, and need for an antidote in case of an overdose.⁴

Due to our nation's opioid crisis and a recent focus on non-opioid alternatives, there has been growing interest in identifying a medication other than fentanyl that will provide safe, short term, satisfactory pain control during first trimester outpatient surgical abortions. Ketamine is commonly used for procedural sedation and analgesia, and it also reduces postoperative pain.⁵ It acts primarily as an N-methyl-D-aspartate receptor antagonist but has some opioid receptor activity.⁶ It is widely used for trauma cases in the emergency department, sickle cell crises, and opioid-induced hyperanalgesia, and is considered a superior agent in the outpatient setting due to its lack of respiratory and cardiovascular depression.⁷⁻¹⁰ In patients with opioid use disorder, ketamine decreases acute and perioperative pain and can reduce postoperative opioid consumption.¹¹⁻¹⁴ Few studies have examined ketamine for surgical abortions. Most studies found improvements in pain control when compared to the paracervical block or remifentanyl.^{15,16}

Previous studies found significant rates of emergence phenomena, where patients experience nightmares or delirium when awakening from ketamine anesthesia, which has likely limited its widespread use in the abortion setting; however, this can be prevented if a benzodiazepine is given at the same time.^{17,18} An ongoing study in Canada is examining ketamine for first trimester surgical abortions with a primary outcome of postoperative pain between oral morphine, IV fentanyl, and IV ketamine.¹⁹ Ketamine deserves further study to determine whether it is an acceptable alternative to a standard opioid-based regimen for surgical abortion.

Research Objectives

Primary objective: To determine if satisfaction with anesthesia among patients receiving ketamine is non-inferior compared to satisfaction among those receiving fentanyl for outpatient first trimester surgical abortions.

Secondary objectives:

1. To determine if postoperative pain differs among participants receiving ketamine versus fentanyl.
2. To determine the amount of additional pain medication needed in those receiving ketamine versus fentanyl.
3. To assess provider satisfaction with anesthesia for those receiving ketamine versus fentanyl.
4. To compare the time to discharge between those receiving ketamine versus fentanyl.
5. To compare pain on postoperative day 1 for those receiving ketamine versus fentanyl.
6. To assess the amount of opioid used 1 week postoperatively for those receiving ketamine versus fentanyl.

Hypothesis: Satisfaction with anesthesia among individuals receiving ketamine will be non-inferior to satisfaction among those receiving fentanyl during first trimester abortions.

Outcomes:

1. Primary outcome: patient satisfaction with anesthesia measured using the Iowa Satisfaction with Anesthesia Scale (ISAS) measured either 30 minutes postoperatively or at time of discharge if less than 30 minutes
2. Secondary outcomes:
 - a. Postoperative pain using a 100mm visual analog scale (VAS) measured either 30 minutes postoperatively or at time of discharge if less than 30 minutes
 - b. Additional pain medication administered by anesthetist after standard loading dose for each arm

- c. Provider satisfaction with anesthesia of patient during procedure on a 100mm VAS
- d. Time from completion of procedure to discharge
- e. Pain on postoperative day 1 measured on a 100mm VAS using a text message link to an online RedCap survey
- f. Patient satisfaction with anesthesia on postoperative day 1 measured using ISAS
- g. Quantity of opioids used 1 week postoperatively using a text message link to an online RedCap survey
- h. Adverse events and severe adverse events

Overall research question: Is ketamine a satisfactory alternative to fentanyl for pain control during first trimester outpatient surgical abortions?

Additional data to be collected:

1. Sociodemographic and clinical data: age, race/ethnicity, gravidity, parity, gestational age, prior vaginal delivery, prior surgical abortion, level of menstrual symptoms, anxiety or depression, previous or current use of opioids.

Design and Methods

Research Design and Methodological Approach

This will be a randomized controlled noninferiority trial of IV ketamine versus IV fentanyl for pain control during first trimester surgical abortions. We will recruit 84 participants from a local abortion clinic with two locations. Our team has an established relationship with this clinic, CRC, with multiple University of Washington Complex Family Planning faculty members and three fellows currently providing care at this clinic, and several successful research collaborations in the past.

Study Population

Participants for this study are women 14 years or older, recruited from CRC, who present for an induced surgical termination of pregnancy up to 13 weeks 6 days gestation. This upper gestational age limit was selected because misoprostol is utilized for cervical ripening starting at 14 weeks per clinic protocol, and pretreatment with misoprostol may alter procedural pain and satisfaction.

The following inclusion and exclusion criteria apply:

Inclusion Criteria:

- Aged 14 years or older

- Voluntarily requesting surgical pregnancy termination
- Intrauterine pregnancy up to 13 weeks 6 days by transabdominal or transvaginal ultrasound performed on day of procedure
- Eligible for suction curettage
- English or Spanish speaking
- Able and willing to give informed consent and agree to terms of the study

Exclusion Criteria:

- Age less than 14 years
- Reaspiration procedure or failed medication abortion
- Early pregnancy loss
- Alcohol use disorder or acute alcohol intoxication
- Currently incarcerated
- Gestational age 14 weeks or more
- Requesting a specific pain regimen
- Premedication with misoprostol
- Contraindications or allergies to ketamine or fentanyl

ISAS is a validated tool used to measure satisfaction with monitored anesthesia care itself, not the perioperative experience.²⁰ Participants answer 11 questions with scores ranging from -3 to +3, and the mean score gives a quantitative measure of a patient's satisfaction. Previous studies have shown 0.6 on ISAS to be a significant difference, and that scores have a standard deviation of 0.87.²¹ Thus, we calculated our sample size with a noninferiority margin of 0.6, standard deviation of 0.87, 80% power, one-sided type 1 error of 0.025, and inflated this number by 10% to account for potential dropout for a total sample size of 84 patients. We will compare mean scores using the student's t-test. All outcomes after discharge will be collected using text message prompts, which will link to a REDCap survey. Alcohol use disorder and acute alcohol intoxication will be defined by the DSM-5 criteria and will be determined by the study personnel prior to consenting the patient.

Subject recruitment and allocation

On the day of the procedure, eligible women will be introduced to the study by research personnel who have been trained in the recruitment process at the study site. Recruitment will continue until the required sample size of 84 is attained. Patients will be introduced to the study after the decision to undergo a surgical abortion has been made. Patients will be informed that they will receive the same care whether or

not they choose to participate in the study, and that they can remove themselves from the study at any point in time.

After establishing that all inclusion criteria are met, patients will receive detailed information about the study and if interest continues, sign a UW IRB-approved written consent available in English and Spanish. Patients will be allowed to ask all questions about the study prior to enrollment and will be asked to briefly summarize the study prior to signing the consent form to ensure comprehension. The abortion providers will be experienced attending physicians and fellows (including the study investigators). A recruitment log will track the number of patients who were approached about the study and will note how many were excluded or declined entry. While there is no minimum gestational age required for study participation, patients must have a documented measurable intrauterine gestational sac per standard practice at the study site.

All providers will have received information about this study prior to enrollment. Providers will be read a verbal consent form and will give verbal consent to participate in the study.

Randomization and allocation concealment

Just prior to starting the procedure, after written consent to participation in the study has been obtained, the subject will be randomized to a treatment group using a predetermined computer-generated blocked randomization (block size of 6) and will be allocated using sequentially numbered, opaque, sealed envelopes. Patients will concurrently be assigned a unique study ID number. Study staff at UW will generate the randomization sequence and prepare the envelopes. The randomization scheme linking patients to their unique study ID will be kept in a password-protected excel spreadsheet. Study investigators will not have access to this password. For data analysis, a member of the study team responsible for randomization concealment will provide the primary investigator with blinded allocation information.

Description of the drugs and devices to be studied

Clinicians including certified registered nurse anesthetists (CRNAs), advanced registered nurse practitioners (ARNPs), and abortion providers will be able to provide additional medications if needed.

Ketamine:

Ketamine is a nonbarbiturate dissociative anesthetic. It acts primarily as a noncompetitive N-methyl-D-aspartate and glutamate receptor antagonist and a partial agonist on opiate mu receptors. It can be used

alone or as an adjunct to other medications for pain relief or as a pre-anesthetic to other general anesthetic agents. Due to its unique properties, ketamine can be used during painful procedures by causing sedation and analgesia. It is an ideal medication for patients with bronchospasm due to its bronchodilatory properties. It is metabolized by the liver and has a half-life of approximately 45 minutes. The initial dose is 1-4.5 mg/kg administered intravenously over 60 seconds with almost immediate onset of action. When given in high doses, negative emergence phenomena may occur. This can be prevented by coadministration of a benzodiazepine, such as midazolam. Allergic reactions to ketamine are rare. Common side effects include nausea, vomiting, dizziness, diplopia, drowsiness, dysphoria, confusion, and negative emergence phenomena. Ketamine is contraindicated in those who are hypersensitive to the drug, chronic alcoholics or acutely alcohol-intoxicated patients, and in patients with schizophrenia.⁵ Because alcohol acts as a synergist to ketamine's physiologic effects, the combination of ketamine and alcohol can potentially be lethal. For the purposes of this study, patients will receive an initial loading dose of 200-500mcg/kg IV ketamine over 2 minutes, which will then be repeated q5m until appropriate analgesia is achieved. The total amount of ketamine given will not exceed 30mg.

Fentanyl:

Fentanyl is a strong synthetic opioid. It acts primarily as a mu-selective opioid receptor agonist and can also activate delta and kappa receptors. It can be used as a sedative, to treat chronic pain, or as premedication for procedures. It is similar to morphine but 50-100 times more potent. It is metabolized by the liver. The initial dose for analgesia is usually 100 mcg IV. When given in high doses, fentanyl can cause respiratory depression leading to arrest, and overdose can be lethal. Naloxone, an opioid drug antagonist, can be used to treat a fentanyl overdose. Common side effects include euphoria, confusion, drowsiness, nausea, visual disturbances, and constipation. Severe side effects include dyskinesia, hallucinations, delirium, addiction, loss of consciousness, and hypotension. Fentanyl is contraindicated in patients who are hypersensitive or intolerant to the drug, have respiratory depression or obstructive airway disease, or in patients with liver failure.²² For the purpose of this study, patients will receive an initial loading dose of 0.5-1mcg/kg IV fentanyl over 2 minutes, which will then be repeated q5m until appropriate analgesia is achieved.

Admission procedure

Following determination of eligibility and collection of demographic information by research personnel and completion of informed consent, participants will complete a pre-procedure survey to collect baseline characteristics and baseline pain and be randomized into a specific arm of the study and be concurrently assigned a participant ID number as described above. The document linking the participant ID number to

the subject's name will be stored in a password-protected document separate from the document linking the randomization to the participant ID number. The anesthetist will open the next available sequentially numbered, opaque, sealed envelope, which contains the participant ID number and the study allocation, either IV ketamine (study arm) or IV fentanyl (control arm). The anesthetist will thus be the only individual to know the participant's randomization. All others will be blinded. Per clinic standard, all participants will receive premedication with 500 mg oral naproxen and 4 mg ODT ondansetron prior to their procedure. All patients receiving sedation are asked to be NPO preoperatively. All participants in this study will receive 2mg IV midazolam, which is standard clinical practice. If the participant is assigned to the ketamine arm, the anesthetist will follow the ketamine administration protocol as detailed above. If the participant is assigned to the fentanyl arm, the anesthetist will follow the fentanyl administration protocol as detailed above. Per protocol, the provider will communicate with the anesthetist if more pain medication is needed, such as if the participant is moving, reporting pain, or otherwise not tolerating the procedure. These additional medications will be documented and collected as secondary outcomes.

The procedures will be performed in accordance with the study design which is consistent with standard clinical procedure. Paracervical block will be administered with 20mL of 1% plain lidocaine: 2mL injected into the anterior cervical lip prior to tenaculum placement, 8mL injected paracervically superficially at 2, 4, 8 and 10 o'clock, and the remaining 10mL injected intracervically at 4 and 8 o'clock. Next, the provider will serially dilate the cervix to the number of mm equivalent to or one mm more than the patient's gestational age in weeks (i.e. to 8 mm at 8 weeks 0 days to 8 weeks 6 days gestation), and a corresponding size suction cannula will be used. At our study site, up to a gestational age of 9 weeks 6 days, manual vacuum aspiration is generally performed, and beyond this gestational age electric vacuum aspiration is more common.

In order to minimize variability in procedures, all procedures are performed by an experienced provider (attending physician or complex family planning fellow). No medical students or residents will perform procedures for study participants. The research personnel will collect pre-procedure information from the participant in a private counseling or waiting room. After the procedure, either at time of discharge (if less than 30 minutes) or at 30 minutes (if not yet discharged), research personnel will assess the participant's level of postoperative pain on a 100mm VAS and have the participant complete the ISAS. The anesthetist will record additional pain medications given outside of the study protocol. The provider will be asked their level of satisfaction with the participant's anesthesia on a 100mm VAS. The research personnel will note time to discharge after procedure completion and any adverse events. Per clinic standard, all patients

will be discharged with 30 tablets of naproxen 500mg and 5 tablets of oxycodone 5mg. Patients are instructed to use their naproxen first for pain and to use the oxycodone only for breakthrough pain.

Follow up procedure

All patients will be contacted via text message on postoperative day 1 with a unique link to a REDCap survey assessing their pain on a 100mm VAS and their satisfaction using ISAS. Satisfaction will be asked again to compare responses on the day of the procedure versus on postoperative day 1. Previous research has shown significant variation in what people remember about their procedure, and thus assessing satisfaction on postoperative day 1 is equally as important as assessing on the day of the procedure.²³ They will then be sent a text message on postoperative day 7 with a unique link to a separate REDCap survey assessing their pain on a 100mm VAS and how much opioids they required in the week following the procedure. As patients are instructed to use oxycodone only for breakthrough pain, this is another measure of pain and will give us more information about the severity of their pain.

Criteria for discontinuation

Patients may choose to withdraw from the trial at any time on their own request for any reason; the reason for withdrawal will be recorded in detail. No further data will be obtained from the patient once withdrawal occurs. Any data obtained up to this point will be analyzed in accordance with intention to treat analysis.

If at any point serious adverse events related to the study protocol occur, these will be reported to the principal investigator and thoroughly investigated. The UW IRB has the authority to request that the treatment groups be unblinded to ensure there is not overwhelming evidence of harm by the study protocol.

Data management

All patient data will be kept confidential. A unique patient study identification number will be placed on the data forms. No patient names will be included with the study data. Study identifiers kept in a password protected Excel spreadsheet will be assigned to each patient to protect confidentiality. Patient identifiers will be stored separately from the data files on the primary investigator's password-protected computer. Only the study investigators will have access to this identifier list.

Data analysis

Data will be extracted and entered into SPSS. Analysis will be performed with the blinded data. All above listed variables will be analyzed in an intention to treat approach.

The sociodemographic profiles of the two study groups will be compared using descriptive statistics (chi-squared for nominal data and student's t-tests for continuous data) to ensure successful randomization. Means of continuous variables (satisfaction, pain, age, gestational age) will be compared with a two-sided student's t-test. Data of categorical variables will be compared with a chi-square test. A p-value of <0.05 defines statistical significance. We will perform subgroup analyses by parity and gestational age, which are factors that may affect pain and satisfaction.

Possible Limitations

Our study population will likely be representative of abortion-seeking clients in Washington state, which may be less diverse than the population of abortion-seeking clients throughout the United States. This may limit the generalizability of our findings. Additionally, not all clinics throughout the United States routinely prescribe oxycodone upon discharge, and thus if we find a reduction in postprocedural opioid usage, this may not benefit all clinics.

Timeline

The study will be conducted at CRC in Renton and Tacoma, Washington. Study procedures will be initiated following approval of the protocol by the institutional review boards at University of Washington and CRC. We anticipate receiving approval by January 2021.

Given the current volume of first trimester abortion procedures at these sites and enrollment rates in past trials at these clinic locations, we anticipate that it will require approximately 12 months to complete enrollment. After enrollment, we will have 6 months to complete data analysis or to finish enrollment for the study if clinical volume or study participation is low.

Use of Research Results

The results of this study will be presented during the University of Washington's Department of Obstetrics and Gynecology Resident and Fellow Research Day. They will also be presented to the Society of Family Planning community at the Complex Family Planning Fellowship Annual Meeting. Finally, the results of this study will be submitted for publication in one of the obstetrics and gynecology specific journals. The study will meet criteria to be included in the Cochrane review updates for pain control in first trimester abortion.¹

Results of this RCT will demonstrate whether or not ketamine is a satisfactory alternative to fentanyl for analgesia for first trimester outpatient surgical abortions or management of early pregnancy failures. If it is shown to be a satisfactory alternative, this would significantly impact the nation's opioid crisis as clinics could start using ketamine as their standard analgesic rather than fentanyl. We may also find that ketamine reduces postoperative opioid use, in which case this will even further impact the nation's opioid crisis and result in less opioid use and addiction related to abortion care. Due to its unique mechanism, ketamine may also be an important alternative for patients with substance use disorders, specifically opioid use disorders. There has also been interest in IM and intranasal (IN) ketamine, and this study would guide future investigations into alternative forms of ketamine to be used in lower resource outpatient settings who do not have the ability to have IV access. Results of our study will potentially guide the approach to pain management for other outpatient gynecological procedures.

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