Low Dose Ketamine Infusion for Analgesia in the Emergency Department to Reduce Side Effects

Study Protocol and Analysis Plan

NCT05518877

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Study Title: Low Dose Ketamine Infusion for Analgesia in the ED to Reduce Side Effects: A Double Blind, Double Dummy Randomized Controlled Trial

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1. Purpose of Study

Research has shown low dose ketamine (LDK) Intravenous push (IVP) (0.3mg/kg) to have equivalent pain reduction in moderate to severe acute pain in the Emergency Department (ED) when compared to standard of care of morphine IVP (0.1mg/kg). Ketamine has been shown to produce side effects in these studies, including dizziness, feeling of unreality and mood changes. There were no unexpected side effects or adverse events during this trial.[1] Another study compared IVP with a slower infusion of LDK and showed a decrease in side effects while maintaining similar analgesic efficacy. This trial found increased feelings of unreality for the IVP group (difference of 37.5%) as well as increased rates of sedation.[2]

In clinical practice, increasing the time/duration of the infusion has resulted in a decrease of reported side effects from patients while still maintaining analgesia. There have been no studies done to prove that there is a further reduction in side effects with a longer LDK infusion. We believe that increasing the infusion time to greater than 15 minutes will reduce the frequency and intensity of expected side effects of ketamine felt by recipients and allow for further use of ketamine as a non-opiate analgesic in the ED.

<u>Overall aims of project:</u>

1. Reduce overall incidence and severity of known side effects of low dose ketamine when given over 30 minutes versus 15 minutes.
2. Maintain adequate pain control, as determined by a Visual Analogue Score (VAS) of ≤5 cm (50mm) at 30 minutes after start of ketamine infusion.

Hypothesis: Slow infusion of LDK over 30 minutes will provide adequate pain control (as defined by VAS score of ≤5 cm (50mm)), and reduce incidence and severity (by at least 20% or 1 point on Side Effects Rating Scale for Dissociative Anesthetics [SERSDA] scale) of known side effects when compared to LDK given over 15 minutes in moderate to severe acute pain for patients presenting to the ED.

2. Background and Rationale

Ketamine is a phencyclidine derivative and functions as an antagonist of N-methyl-D-aspartate receptor (NMDA).[3] Painful stimuli activate nociceptive neurons triggering the release of glutamate, which attach to NMDA receptors in the dorsal horn of the spinal cord.[4] This triggers a cascade responsible for central sensitization and secondary hyperalgesia, also known as the "wind-up" phenomenon, making pain relief harder to achieve [3,4]. NMDA receptors are also known to be involved in the development of opioid tolerance.[4]

Ketamine is FDA approved for anesthesia and procedural sedation but is known to have a long history of off label uses such as analgesia and treatment of depression. While the medication is not FDA approved for analgesia, it is not restricted for sole use as an anesthetic agent. It is generally accepted that off-label use of medications is acceptable at the sole discretion of the provider. Off-label use has spurred increase in research and has even led to FDA approval in the past, notably for intranasal esketamine for treatment-resistant depression in 2019.[5] Many of the following articles show that ketamine can be used as a safe alternative for analgesia in the hospital setting, notably the Emergency Department.

Ketamine at low (sub-dissociative) doses of 0.1-0.3mg/kg, has been shown to improve pain scores as well as reduce perioperative opioid consumption with minimal side effects.[4] At these sub-dissociative doses, it has produced hemodynamically stable anesthesia and analgesia with minimal measurable cardiovascular, respiratory, or gastrointestinal side effects.[3,4]

In 2015, a prospective, randomized double blind trial compared low dose ketamine to morphine for analgesia and showed promising results. Patients received either 0.3mg/kg of ketamine or 0.1mg/kg of morphine for acute moderate to severe pain to study efficacy and safety profile. Similar rates of reduction in pain were found in both groups at all time points. The ketamine group had more reported side effects including dizziness, disorientation, mood changes and nausea at the five-minute mark (73% vs 51%) and at

the fifteen-minute mark (69% vs 31%) but they equalized with the morphine group at the thirty-minute mark (36% vs 33%).[1]

Based on mentioned data, we hypothesized that increasing time for low dose ketamine infusion when used in the ED for analgesia will reduce side effects even further than what prior studies have shown. There are several research papers that support our hypothesis.

A prospective double-blind trial of 40 patients was conducted for acute musculoskeletal trauma pain with treatment groups receiving either intermittent morphine (0.1mg/kg every 4 hours IV) or continuous infusion of subcutaneous ketamine (0.1mg/kg/hr) after an initial bolus (0.25mg/kg). Pain was measured on a 10-point visual analog scale (VAS), along with 4-point sedation score and objective vital signs. There was statistically significant improvement in pain for the ketamine group starting at fifteen minutes which continued to the 24-hour mark. No significant changes in hemodynamics were observed. Two patients in the ketamine group, compared to zero in the morphine group, reported dreams as a side effect after bolus doses. There were significantly higher rates of nausea and vomiting in the morphine group (7 vs 0, $p<0.01$).[6]

A prospective study with 38 patients was conducted to describe the analgesic efficacy and side effect profile of low dose ketamine for acute severe pain in the emergency department (ED). The study trialed a bolus of ketamine (15mg) as intravenous push (IVP) followed by slow infusion (20mg) over 60 min. Patients were offered morphine 4mg as rescue analgesia at the 20-, 40-, and 60-minute marks. Pain was assessed on a 10-point verbal numerical reading scale (NRS), along with vital signs and sedation scores frequently over 120 minutes. At the 60-minute mark, side effect rating scale for dissociative anesthesia (SERSDA) scale was used to assess side effects. Twenty-two patients had clinically significant reduction in pain at 10 minutes. Twenty-five patients had clinically significant reduction at the end of the infusion (60 minutes). Twelve patients did not require or refused adjunct morphine therapy, as pain was adequately controlled throughout the duration of the study. There was a significant proportion of patients that experienced side effects (33 patients, 86%) with a large portion grading them as weak or modest (20 patients, 53%). Thirteen patients (34%) reported side effects as “very bothersome”. The most common side effects were dizziness, fatigue, nausea and feeling of unreality. A large portion of patients (32 patients, 84%) reported they would trial ketamine again for pain management.[7]

A case series looked at 14 patients in an urban ED who received low dose ketamine (0.2-0.4mg/kg) infusions (10-15min) for analgesia. Thirteen patients had received analgesia prior to the ketamine infusion. No patient received rescue analgesia one hour post

infusion. There were no dangerous adverse effects noted. One patient reported tinnitus and uneasiness during the infusion while another reported dizziness.[8]

A recent study conducted in 2017 aimed to show reduction in side effects of LDK by giving it over 15 minutes compared to standard IVP of less than 5 minutes. A total of 48 patients were enrolled and the study showed similar rates of side effects except for overall feeling of unreality, which was significantly higher in IVP group (91.7% vs 54.2%, p=0.008). There were similar decreases in pain scores for each group (p=0.14) with no significant difference in use of rescue analgesia or change in vital signs.[2]

Another study published in 2018 mimicked the previously mentioned trial comparing LDK (0.3mg/kg) IVP (over one minute) and slow infusion (SI) over fifteen minutes, with a primary outcome of decreasing side effects. There were 59 participants that completed the study with a large reduction in psych perceptual side effects noted in SI group (43.4% vs 75.9%). There were also more participants that experienced hallucinations in the IVP group (8 vs 2). There was no difference in analgesic efficacy between the groups.[9]

Trials have shown that ketamine can be used as an adjunct to traditional analgesics with significant opioid sparing effects while maintaining, or even improving, analgesia.

A double blind, randomized, placebo trial was conducted with three groups in 2014. The three groups were morphine plus placebo (MP), morphine plus 0.15mg/kg ketamine (MK15), and morphine plus 0.3mg/kg ketamine (MK3). The purpose of this trial was to assess pain control with less opioid requirement. The study found that all groups had clinically meaningful decreases in overall pain scores. In both ketamine groups, there was a sustained decrease in pain score over two hours. While there were no vital sign abnormalities, there was a higher proportion of patients in the ketamine group that reported side effects, such as dizziness or lightheadedness.[10]

A prospective pre-hospital cohort study in 2009 compared morphine 0.2mg/kg (M) to morphine 0.1mg/kg plus ketamine 0.2mg/kg (MK) in respect to pain, nausea, sedation, and hemodynamics for acute bone fractures. There was a decrease in morphine quantity used when combined with ketamine (13.5 ± 3.2mg vs 7.0 ± 1.5mg). The mean ketamine dose was 27.9 ± 11.4 mg. Significant changes in pain on numeric rating scale were reported in favor of MK (3.1 vs 5.4) along with elevations in BP (167 vs 134). Side effects/adverse effects noted include nausea (4 patients vs 1) and vomiting in MK group (3 patients vs 0).[11]

Based on the information from prior studies, ketamine has been proven to be a potent analgesic even when compared to standard of care morphine. The downside to ketamine

use seems to be due to the side effect profile that is bothersome to some patients. A previous study already showed improvement in side effects, mainly dizziness, when given over a longer period of time (15 minutes). We are hypothesizing that further increasing the administration duration will produce even less side effects while maintaining analgesic properties.

Literature reviews have been done that elaborate on the common side effects of ketamine when given for analgesia. One noted most common events to be nausea, altered mood, psychomimetic effects and headaches when given intravenously for complex regional pain.[12] Another article noted that there seemed to be psychomimetic effects along with hypertension when given for pain control via intravenous infusion, although appeared to improve after infusion was complete.[13] Similar side effect profile in terms of psychomimetic effects has been seen in other studies and include dizziness, blurred vision, vertigo, nausea/vomiting, dysphasia, nystagmus, nightmares or vivid dreams, impaired motor function and memory deficit but like other studies, improves rapidly after infusion is complete. Cardiovascular effects secondary to the catecholamine release after administration have also been documented. The main effects appear to be tachycardia, hypertension and increase in cardiac output and recommend use of cardiac monitoring but do not seem to be long lasting effects.[14]

This study has been determined to be exempt from FDA IND requirements based on all criteria for exemption being met.

3. Study Design

The location of this study will be the Akron City Hospital Emergency Department. The trial will enroll approximately 48 evaluable subjects. An evaluable subject is defined as a subject who completes the entire infusion (30 minutes) and provides a 30 minute VAS and SERSDA score.

This will be an intent to treat prospective, double blind, double-dummy, randomized trial. The primary outcome will be a comparison of side effects of sub dissociative dose ketamine given by slow IV infusion over 15 minutes vs 30 minutes in treatment of moderate to severe acute pain in ED patients. The secondary outcome will be adequate pain control (VAS ≤5 cm(50mm)) and need for rescue analgesia between the two groups.

The control group will receive slow IV infusion of ketamine over 15 minutes. The experimental group will receive slow IV infusion of ketamine over 30 minutes.

If the patient meets all eligibility criteria, they will be consented by study staff members and then randomized to receive ketamine 0.25mg/kg in 100cc normal saline (NS), up to a

maximum of 30mg total dose, as an IV infusion over the specified time, as well as “placebo” 100cc NS over the other time slot.

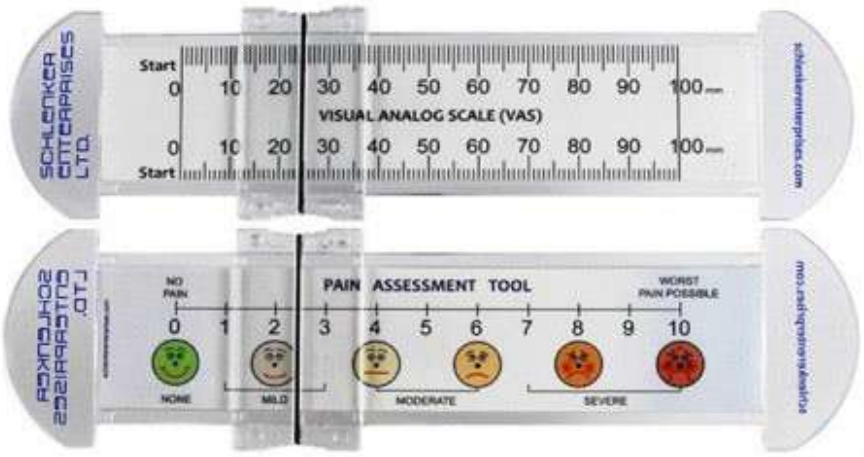
If during the baseline assessment, immediately prior to the start of infusion, the subject reports an improved pain score (VAS < 5 cm(50mm)), the subject will be considered no longer eligible. The infusion will not be administered, and the subject will be removed from the study.

Since the subject was randomized, the group allocation (control or experimental group) for that subject will be reassigned to the randomization block to maintain a total of 48 enrolled (infused) subjects.

Pharmacy staff will provide the study medication in a blinded fashion to the nurse who will use infusion pumps to deliver both study medication and placebo simultaneously. Nursing staff will receive training on administration of the study medication prior to starting the study.

We will measure the side effect profile using the Side Effects Rating Scale for Dissociative Anesthetics (SERSDA) along with the Visual Analog Scale (VAS) (Appendix A).

Visual Analogue Scale scoring is done by asking the subject to mark the spot on the VAS Pain Assessment Tool (0-10cm) to indicate their perception of pain. Following this, the investigator scores the intensity of pain according to the 0-100mm corresponding scale (one instrument i.e., 5cm= 50mm). The VAS is a validated, subjective measure for acute and chronic pain. See below for exact tool that will be used.



Vital signs (heart rate, blood pressure, respiratory rate, and oxygen saturation) will also be obtained at 0, 5, 15, 30, 60, and 90 minutes from the start of the ketamine/NS placebo infusion.

Rescue Medication

At 30, 60 or 90 minutes post start of the ketamine infusion, if the study subject has a VAS score that is between 5-10cm (50-100mm), a **single** dose of both acetaminophen 1,000mg (oral) and ketorolac (15-30mg IV) will be given. If alternative medications are required, the study investigator will be consulted.

NOTE: EPIC recommends a ketorolac dose of 15mg IV if subject weight is less than 50kg or subject age is ≥65 years.

At 30 minutes post start of ketamine infusion, if the study subject has a VAS score that is between 8-10cm (80-100mm), fentanyl will be administered at 1mcg/kg up to 100mcg. (The dose will be calculated by EPIC to correspond to the nearest 0.05cc). If deemed safe and appropriate, the EPIC alert for doses greater than 100mcg may be overridden by the treating physician or study investigator to authorize doses greater than 100mcg (per institutional policy).

If the VAS score remains 8-10cm (80-100mm)) when assessed at 60 and 90 minutes post start of the ketamine infusion, the fentanyl dosing may be repeated.

NOTE: If the VAS score is assessed to be between 8-10cm (80-100mm) at any time point, and ketorolac and acetaminophen have **not** already been administered, ketorolac, acetaminophen and fentanyl may be given at the same time point.

NOTE: Ketorolac and acetaminophen may only be administered once during the study.

Study Termination

If rescue medication is administered, the patient will continue in the study and all data will be collected as outlined in the protocol as ITT (intent to treat).

If the subject experiences side effects which are unable to be managed in order to permit the continuation of the ketamine infusion, it will be stopped. All data will continue to be collected according to the protocol and the subject will continue to be observed for the remainder of the 90-minute study period, unless the subject withdraws their consent to participate.

3.1 Subject Population

Inclusion and Exclusion Criteria

Inclusion criteria:

- Patients 18 years of age or older
- Primary complaint of acute moderate to severe pain on VAS/numeric pain scale (a score of ≥5cm which corresponds to 50mm).
- Pain described as abdominal, flank, back, musculoskeletal, or traumatic chest pain
- Must be alert and oriented times three
- Able to provide informed consent.

Exclusion criteria:

- Pregnant
- Breastfeeding
- Altered mental status
- Known or reported allergy, hypersensitivity, or intolerance to ketamine
- Unstable vital signs (systolic blood pressure <80 or >180mmHg, heart rate <50 or >150 beats per minute, and respiratory rate <10 or >30 breaths per minute)
- History of unstable heart disease, such as arrhythmias, congestive heart failure, or coronary heart disease.
- History of untreated or uncontrolled thyroid disease
- Acute head or eye injury
- Active or current abuse of alcohol or illicit drugs
- Known intracranial hypertension
- Hepatic or renal insufficiency
- Current active manic phase of bipolar disorder
- Active delusions, hallucinations, or schizophrenia
- Patients who have recent fentanyl use within 60 minutes or other analgesic use (opiates) within 4 hours of study enrollment (signing of consent)
- Patients who have enrolled in the study during a previous ED encounter
- Chronic use of opiates (i.e.: fentanyl patch, SR opiates)

It will be at the discretion of the treating ED physician who is taking care of the patient to determine whether the patient is appropriate for the study. If it is determined the patient requires a more urgent form of pain control intervention, the patient will be excluded.

3.2 Study Intervention

Once consented , participants will be randomized to receive 0.25mg/kg (up to a maximum

of 30mg) intravenous ketamine mixed with 100cc normal saline (NS) either over: (1) 15-minute slow infusion (SI) or (2) 30-minute slow infusion.

Each group will receive corresponding placebo of 100cc NS for double dummy design.

The group receiving ketamine over 15-minute SI, will also receive 100cc NS over 30 minutes and the group receiving ketamine over 30 min SI will also receive 100cc NS over 15 min. Ketamine/NS placebo infusions will be delivered via infusion pump. The two infusions are to be given simultaneously so that time zero (0) is the same for both infusions.

Ketamine/NS placebo will be prepared and blinded by pharmacy staff and be administered in a blinded fashion by an ED or Research RN. For the purposes of this study a subject will be considered enrolled once they have received any portion of the investigational product.

Patients may not be enrolled in the study more than one time. They may not be re-enrolled if they present to the ED with acute pain a subsequent time. This is to prevent any bias from forming in the data analysis secondary to the side effect profile of the drug as well as the potential psychotropic effect the drug may have.

3.3 Outcomes/Objectives

The primary objective of this study is to attempt to prove that increasing the length of ketamine administration decreases overall incidence and severity of side effects. The side effects to be monitored include fatigue, dizziness, headache, feeling of unreality, hearing, vision, or mood changes, generalized discomfort, and hallucinations. Our goal is to have at least a 20% decrease in overall scores, which equals to a “1” point decrease on the SERSDA scale. SERSDA measures severity of nine adverse effects based on a 5-point scale from “0” (no adverse effect) to “4” (very bothersome effect).

The primary outcome measure of this study is the reduction of the overall side effects as measured by the Side Effect Rating Scale for Dissociative Anesthetics (SERSDA) at 30 minutes.

The secondary objective is to ensure that adequate pain control (VAS ≤5 cm) is maintained when ketamine administration is prolonged. To do this we will be measuring pain scores on the 100mm VAS at each protocol specified interval (0, 5, 15, 30, 60 and 90 minutes from the infusion start time, which is defined as time zero). Studies have shown that for clinical significance in pain reduction, there needs to be at least a 13mm difference on the 100mm VAS pain scale.[15]

The secondary outcome measure is the severity of self-reported pain on the standard 100mm VAS pain scale (0-100) at 30 minutes.

The need to administer rescue analgesic medication will also be assessed, starting at 30 minutes and again at 60 and 90 minutes post start of the infusion (Time 0).

We will also be monitoring the need for the administration of other interventions to treat ketamine side effects (nausea etc.), as well as vital signs.

The Richmond Agitation Sedation Scale (RASS) (Appendix A) will be used to collect additional data.

Study Schedule

	Time 0 min	**Time 5 min**	**Time 15 min**	**Time 30 min**	**Time 60 min**	**Time 90 min**
VITAL SIGNS	X	X	X	X	X	X
SERSDA		X	X	X	X	X
VAS	X	X	X	X	X	X
RASS		X		X		X

4. Data Analysis/Plan

The sample size of n=24 in each study arm (n=48 overall) was determined to detect a clinically significant median change of one unit in the primary outcome and SERDSA scale, for measuring adverse events. This determination assumes the same standard deviation of 1.2 units with 80% power assuming a two-sided alpha type I error rate of 5% used previously to adequately power the Motov study[2] which was based on the estimated standard deviation from the Andolfatto[16] study. We will enroll stratified by gender (male/female) to ensure equality between the two study groups.

Separate sealed envelopes will be provided to the pharmacist containing the randomization assignment to allow for more comparability between study arms. Each sealed envelope will be identified by gender and patient enrollment number, e.g., 'Male 01', and contain an assignment to either study arm within the envelope. Envelopes for randomized subjects will be stored in the investigational pharmacy. A secondary copy of the randomization assignments will be managed on a secure research shared drive within the Clinical Research Center. Access will be limited to only unblinded study staff. A

maximum enrollment for either gender will be 14 out of the 24 (58.3%) to provide a more balanced gender ratio which is more generalizable to the intended population.

Randomized blocks of 2 and 4 units will be employed within each gender strata to allow for balance across the enrollment period.

Study data will be collected via a REDCap instrument. A randomization number will be assigned and after baseline data is collected, observation and longitudinal data will be captured via a repeated measures survey in REDCap. Time points captured will be baseline (0min), 5min, 15min, 30min, 60min and 90min from the start of the study infusion which is time zero.

Data from this double-blind, double dummy, randomized comparative study will be imported into SPSSv25.0 software (IBM Corp., Armonk, NY) with baseline characteristics summarized by treatment arm. A generalized linear model using an underlying gamma distribution will be employed for all ordinal data including SERDSA outcomes collected at time points before complete resolution to “0”. A mixed model regression will be employed for all continuous outcomes across time with missing data assumed to be random. Boxplots of outcome will also be provided at each study time point stratified by study arm. Additionally, the rates of adverse events will be summarized using frequencies and percentages and compared between study arms via Fisher’s exact or Pearson chi-square tests depending on cell sample size distribution.

Variables collected during the study include patient demographics (age, sex, pain type/location), vital signs on presentation as well as during specified times (heart rate, blood pressure, respiratory rate, and oxygen saturation), Visual Analogue Scale (VAS) scores, SERSDA scores[17], Richmond Agitation-Sedation Scale (RASS) and time to rescue analgesia.

If patients withdraw from the study prior to medication administration, they will not be included in the final data set. If they decide to withdraw while medication is being administered or after the completion of the infusion, but during the follow-up period of 90 minutes, they will be in the final data set and shown on the diagram as withdrawn.

There may be CITI trained and CRC Credentialed medical students, ED residents and faculty members who will help with the enrollment process and data collection.
Data for this study will be collected in REDCap. REDCap is a HIPAA compliant clinical electronic data capture system. All patient records entered into REDCap will have identifiers removed and will be given a unique study-specific code. Patient identifiers (patient name, DOB, MRN) with codes will be stored separately in an Excel spreadsheet located in a secure folder on the Summa G:/ drive, accessible only to authorized study personnel. Only authorized study personnel will be given access to the data collection sheet in REDCap. Multi-factor authentication (MFA) security is used to access the

REDCap platform. Full audit trails are kept within REDCap.

All study related data will be kept in the CRC for a minimum of 6 years after study completion, unless the study is published. If published, all study data should be kept for 10 years, per Summa policy.

5. Data Safety and Monitoring

Study data will be reviewed for safety and interim analysis will be completed at the following study subject accrual points: 3 patients, 6 patients, 12 patients, 24 patients and 40 patients. The review committee will consist of an odd number of physicians, with a minimum of one physician who is not associated with the Summa Emergency Department. During review, if it is determined the majority of study subjects (75%) did not experience a clinically significant reduction in pain (which is an improvement of 13mm on the 100mm VAS scale) the study will be stopped. The results of each safety monitoring review will be summarized and submitted to the IRB.

CRC staff will be responsible for collecting and communicating AE's, SAE's, UAP's, and protocol deviations per institutional policies.

CRC staff will be responsible for data collection and data entry into REDCap. Data will be reviewed for accuracy and completion on a regular basis.

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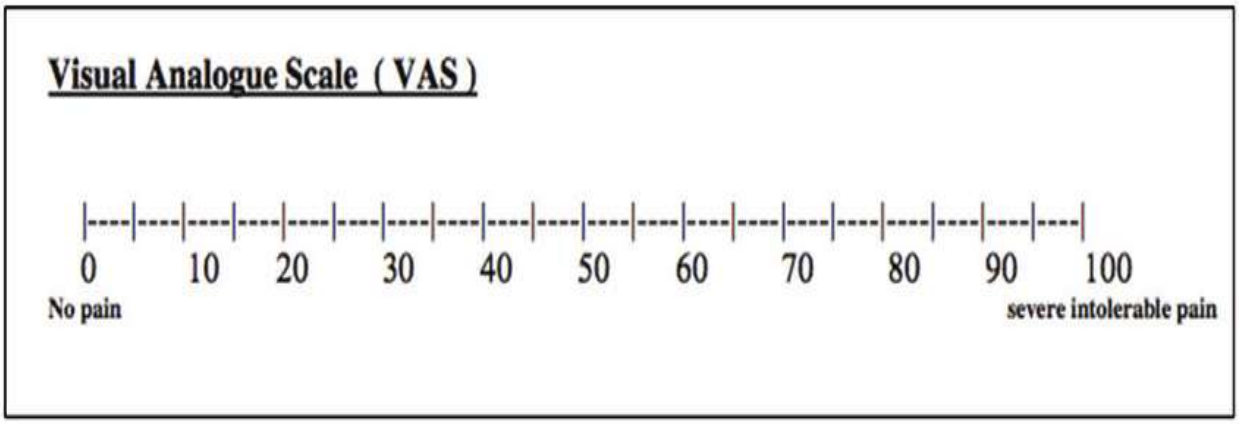
APPENDIX A

Visual Analogue Scale (VAS)



Side Effects Rating Scale for Dissociative Anesthetics (SERSDA) Scale

Side Effects	Severity	Scale
Fatigue		0, No Change
Dizziness		1, Weak
Headache		2, Modest
Feeling of Unreality		3, Bothersome
Change in Hearing		4, Very Bothersome
Change in Vision		
Mood Change		
Generalized Discomfort		
Hallucination		

The Richmond Agitation Sedation Scale (RASS)

+4	Combative	violent, immediate danger to staff
+3	Very Agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous
0	Alert & calm	
-1	Drowsy	Not fully alert, but has sustained awakening to *voice* (eye opening & contact ≥ 10 sec)
-2	Light sedation	Briefly awakens to *voice* (eye opening & contact < 10 sec)
-3	Moderate sedation	Movement or eye-opening to *voice* (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to *physical* stimulation
-5	Unarousable	No response to *voice or physical* stimulation