Title:	**Low Dose Ketamine for Blunt Thoracic Trauma: A Prospective Randomized Trial**
Short Title	Ketamine for Rib Fracture Study
Study Type:	Randomized, double-blinded study of low dose Ketamine infusion (off-label pain control) in patients with 3 or more rib fractures
Protocol Date:	1/13/21

Joseph Farhat, MD
NORTH MEMORIAL HEALTH HOSPITAL

Trauma Services
3300 Oakdale Ave N
Robbinsdale, MN 55422
Phone: 763-581-3700
email: joseph.farhat@northmemorial.com

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ABSTRACT

Introduction:

Thoracic trauma creates a significant burden of morbidity and mortality in those suffering from blunt traumatic injuries. Optimal contemporary management of blunt thoracic injury includes intravenous narcotics, epidural analgesia, and both noninvasive and invasive positive pressure ventilation for those patients that progress to respiratory failure. In 2019, the Medical College of Wisconsin published the first randomized controlled trial evaluating the effects of a low-dose ketamine infusion on pain scores (primary outcome), opioid analgesic use, epidural rates, and pulmonary complications in adult and elderly patient with 3 or more rib fractures. Their results demonstrated decreased oral morphine equivalents (OME) utilization, but only in severely injured patients (ISS>15). Their results were otherwise equivocal and additional study was recommended. Low dose ketamine therapy has been examined in multiple studies as a therapeutic adjunct for postoperative analgesia (FDA off-label use). In this capacity it has been shown to significantly lower pain scores and reduce narcotic requirements. We hypothesize that low-dose ketamine infusion will decrease narcotic use (OME), improve pain control, and improve pulmonary morbidity in patients who suffer blunt chest trauma.

Objectives:

Primary: Determine if addition of a low-dose ketamine infusion decreases narcotic analgesic use (OME) in trauma patients with ≥ 3 rib fractures.

Secondary: Determine if adjunctive low-dose ketamine infusion in trauma patients with ≥ 3 rib fractures results in: improved pain control, fewer pulmonary complications, and decreased hospital (or Intensive Care Unit, if applicable) length-of-stay.

Study Design:

- Randomized controlled double-blinded trial: Patients will then be randomized into one of two study groups. Both groups will receive a normal saline infusion for 48 hours of therapy. The treatment group will have ketamine added to their saline infusion via blinded pharmacy protocol to receive continuous infusion of ketamine at 0.1mg/kg/hour. The control group will receive only normal saline. Administration will occur via piggyback infusion in accordance with nursing policy.

Setting/Participants:

- North Memorial Health Hospital: patients on 5S – TNICU and 6W – Trauma Floor
- 50 people will take part in this study. 25 study subjects will receive an infusion of ketamine and 25 will receive a saline infusion.
- Patients 18 years of age or older with 3 or more rib fractures admitted to North Memorial Health Hospital will be considered for the study.

Study Interventions and Measures:

- Ketamine low-dose infusion administered at 0.1 mg/kg/hr for 48 hours as an adjunct to standardized rib fracture management interventions as outlined in facility-approved Guidelines for Rib Fracture Management (see Appendix A)
- The primary study outcome will be amount of narcotic used over the 48 hour study period (expressed as morphine equivalents).
- Secondary outcome measures will include: need for endotracheal intubation or non-invasive positive pressure ventilation, oxygen requirements, daily incentive spirometer values, daily forced vital capacity measurements, and subjective patient pain ratings.
- Other outcomes measured will be Intensive Care Unit stay, total hospital length of stay, and adverse medication effects.

1 BACKGROUND INFORMATION AND RATIONALE

Thoracic trauma creates a significant burden of morbidity and mortality in those suffering blunt traumatic injuries. Thoracic injuries are found in approximately 60% of multiply injured patients[1]. In all demographics with blunt chest trauma, pulmonary complications occur in over a third of cases with a pneumonia rate up to 30%[2]. Thoracic injury is responsible for 25% of blunt trauma mortalities[1,3]. In patients over 65 years old, morbidity and mortality rates are much higher[2]. Optimal contemporary management of blunt thoracic injury includes IV narcotics, epidural analgesia, and both noninvasive and invasive positive pressure ventilation for those patients that progress to respiratory failure[2,3]. Multi-modal pain control therapies are considered standard of care for these patients[4]. However, certain modalities such as use of opioids are well known to have unwanted side effects. Use of epidural catheters, although conditionally recommended as a beneficial treatment, is not always available and may be contraindicated in certain patients[4].

A single randomized controlled study has been published, in 2019 by the Division of Trauma and Acute Care Surgery at the Medical College of Wisconsin, evaluating the effects of low-dose ketamine infusion on pain, opioid use, pulmonary complications, and epidural use in adult and elderly patients with 3 or more rib fractures. Their results demonstrated a statistically significant reduction in oral morphine equivalent (OME) use in patients with injury severity scores of greater than 15[8,9]. These findings were encouraging but warrant additional study.

Low dose ketamine infusion has additionally been examined in multiple studies as a therapeutic adjunct for postoperative analgesia[5-7]. In a recent meta-analysis, low dose ketamine infusion for up to 48 hours postoperatively significantly reduced pain scores and decreased opioid consumption by 40% with no major complications[6]. In patients undergoing thoracotomy or sternotomy, a randomized study demonstrated 50% lower

morphine consumption with no major side-effects in those started on a low dose ketamine infusion in addition to a morphine PCA[7].

Adequate pain control remains a crucial element in management of blunt thoracic trauma. By providing effective analgesia, the provider may successfully limit the increased morbidity and mortality inherent in the progression to respiratory failure[2]. The postoperative literature, including a study specific to chest surgery, demonstrates a clear effect in improving analgesia and decreasing narcotic usage with no major complications[5-7]. We hypothesize that low dose ketamine infusion will improve pain control, decrease narcotic use, and improve pulmonary morbidity in patients who suffer blunt chest trauma.

This study will be conducted in full accordance with all applicable North Memorial Medical Center Research Policies and Procedures and all applicable Federal and state laws and regulations. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with North Memorial Health Hospital IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

The purpose of the study is to determine if adjunctive low-dose ketamine infusion enhances pain control and decreases respiratory complications in adult patients with 3 or more rib fractures.

2.1 Primary Objective

Primary: Determine if adjunctive low-dose ketamine infusion results in decreased narcotic usage.

2.2 Secondary Objectives

The secondary objectives are to:

- Determine if low-dose ketamine infusion as an analgesic adjunct leads to improved pain control as measured by subjective patient pain ratings
- Determine if low-dose ketamine infusion as an analgesic adjunct leads to decreased pulmonary complications as evidenced by decreased rates of respiratory infections, decreased rates of intubation or use of non-invasive positive pressure ventilation, and/or stable to improving pulmonary function testing
- Determine if low-dose ketamine infusion as an analgesic adjunct leads to decreased Intensive Care Unit (as applicable) and/or hospital length of stay

3 INVESTIGATIONAL PLAN

3.1 Study Design

The study will be conducted as a prospective, randomized, double-blinded, placebo-controlled study comparing saline infusion with low-dose ketamine, versus saline infusion alone.

3.2 Study Phases

3.2.1 Screening Phase

Patients will be identified based on initial Emergency Room documentation, initial imaging studies, and/or admission History and Physical, or initial Consultation by the Trauma Services Provider. Prospective study participants will be selected based on the inclusion/ exclusion criteria below. They will be approached after admission regarding study participation via a face to face contact. Final screening and consent will be conducted by trained personnel from the Trauma Services department.

Informed consent will be obtained prior to conducting any study-related activities beyond the typical medical care for the patient's condition.

3.2.2 Treatment Phase

The treatment phase will be initiated as soon as the subject has been identified as meeting inclusion criteria and consented to participate. Pharmacy will be notified of inclusion in the study and the infusion bag prepared based on a pre-determined randomization protocol (see Appendix B, Sample Randomization Schedule). The medication, either normal saline or normal saline with low-dose ketamine, will be administered by the Registered Nurse (RN) following nursing medication administration policy. Nursing staff will reorder infusion bags from the Pharmacy per medication policy as needed. The infusion will be discontinued at the end of the 48 hour period.

3.3 Allocation to Treatment Groups and Blinding

Study drug will be ordered within EPIC by selecting "Rib Fracture Study Drug". The research pharmacist will obtain information about the patient (Name, MR#, and weight) and will then consult the Randomization Schedule to determine whether the 100 mL Saline Infusion Bag will receive 100 mg of ketamine (Ketamine Infusion Subject) or no added medication (Saline Infusion Subject). The Study Drug Bag will be released with a label that includes: Name of Study, Study Subject #, Patient Name, Pt MR#, Pt DOB, and INFUSION RATE. (Note: infusion rate is 0.1 mg/kg/hr and concentration of standard ketamine infusion bag is 1 mg/mL. That is, 100 mg of ketamine added to 100 mL saline).

Bags will be labeled as Study Drug (using consecutive numbers, between 1-50, that correspond to the randomization envelope), but the patient, nurses, physicians, and all others caring for the patient will be blind with respect to the contents of the infusion bag. Pharmacy personnel would be the only individuals with knowledge of the infusion bags and would not

communicate with caregivers once the medications leave the pharmacy. See unblinding section below for further detail.

3.4 Study Duration, Enrollment

3.4.1 Duration of Study Participation

Study subjects will receive the ketamine versus normal saline infusion for 48 hours after identification and enrollment. Information from their entire hospital course will be evaluated as related to the objectives as discussed above.

Recruitment will stop when 50 subjects are successfully enrolled.

3.5 Study Population

3.5.1 Inclusion Criteria

1) Males or females 18 years of age or older
2) Diagnosis of 3 or more acute rib fractures related to blunt traumatic chest injury.
3) Able to undergo consent procedure and give valid consent, or availability of family member to provide consent for the study

3.5.2 Exclusion Criteria

1) Age <18 years
2) Cognitively impaired
3) Pregnant or lactating females.
4) Glasgow Coma Score (GCS) of ≤ 14 at time of admission
5) Evidence of increased intraocular pressure
6) Presence of acute coronary syndrome
7) Diagnosed moderate to severe traumatic brain injury
8) Evidence of uncontrolled intracranial hypertension
9) History of seizures or stroke
10) History of severe psychiatric disorders
11) Allergy to ketamine
12) Currently being treated, prior to admission, with opiate agonist/antagonist therapy

13) Presence of poorly controlled hypertension, cardiac arrhythmias, and/or tachycardia on admission

14) Subjects who, in the opinion of the Investigator, may be inappropriate for study participation.

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

3.6 Subject Completion/Withdrawal

Study participation is considered completed when they have received the 48 hours of medication infusion.

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the investigator and/or attending provider for lack of adherence to study treatment, adverse events, or due to other circumstances in which patient treatment may be impeded by continuation of the study treatment.

The providers caring for patients enrolled in the study may withdraw subjects from the study if they have concerns about possible administration of ketamine. Caregivers should make clinical decisions based on the idea that patients are receiving ketamine, since the randomization code will not be broken.

3.7 Safety Evaluation

Subject safety will be monitored for adverse events as outlined by the Ketamine, Low Dose for Analgesia, Adult Order Set. This includes monitoring heart rate, blood pressure, and respiratory rate 15 minutes after starting infusion and every 4 hours thereafter while receiving infusion. The ordering provider will be notified if systolic blood pressure is less than 90 or greater than 180, if heart rate is less than 60 or greater than 120, or if the respiratory rate is less than 10 during infusion. Mental status will also be monitored during normal nurse rounding and the ordering provider notified if sedation, hallucinations, cognitive changes, dysphonia, anxiousness, and/or restlessness are observed.

4 STATISTICAL CONSIDERATIONS

A power analysis was used to inform the investigators about appropriate sample size. Numerous studies of ketamine infusion for post-op analgesia suggest that the morphine equivalent opiate use is decreased from 17% to 46% (average decrease 34.1%, *Pain Medicine 2014;383-403)*. Assuming a mean baseline narcotic use of 32+10 mg statistical power (alpha = 0.05, 2-tailed test) to detect a 15% decrease in narcotic use is 92.4%. Assuming a similar baseline opioid use there would be an 80.7% chance of observing a 12.5% in morphine equivalents with a 1-tailed analysis. Therefore, the investigators feel confident that the likelihood of a Type II error would be minimal with the proposed sample size of 50.

Total narcotic analgesics administered during the 48 hour study period will be abstracted from the electronic medical record and converted to morphine equivalents (with aid of pharmacy or morphine equivalent calculator, for example: http://www.agencymeddirectors.wa.gov/calculator/dosecalculator.htm). Mean + standard deviation morphine equivalents for ketamine and placebo groups will be compared. Descriptive categorical and continuous characteristics of each cohort will be tabulated and compared. Categorical variables (including, gender, age > 55, use of epidural catheter, operative fracture stabilization, and disposition) will be analyzed using Chi-square tests. Continuous variables will be compared using ANOVA, multiple linear regression, or t-tests as appropriate. Continuous variables to be abstracted, tabulated, and compared including: age, ICU length of stay, hospital length of stay, number of fractured ribs, Injury Severity Score (ISS), negative inspiratory force (NIF), and vital capacity (VC).

4.1 Efficacy Analysis

The primary analysis will be based on an intention to treat basis (i.e., randomization to study arm and at least 1 hour of study drug infusion) and will include all subjects enrolled into the study. The primary endpoint will be the total dose of all narcotic analgesics (converted to morphine equivalents) received during the 48 hour period after the patient begins study drug infusion. (Note, for the purposes of the study initiation of study drug infusion starts the 48 hour window for narcotic use monitoring).

Secondary endpoints will include examination of hospital, and/or ICU, length of stay, pulmonary function studies (NIF and VC), subjective pain scores (visual analog pain scores from electronic medical record), and the incidence/number of adverse events (e.g., ICU readmission, pneumonia, bronchoscopy, etc.).

4.2 Safety Analysis

No specific safety analysis is planned, because ketamine is an approved medication for adjunctive treatment of post-operative and other types of surgical pain. All subjects will be monitored for any adverse events per the usual care parameters. Such events are noted by caregivers, care adapted appropriately if concern related to study drug, and findings and interventions documented in the electronic health record.

4.3 Interim Analysis

No interim analysis is planned for this study. All subjects will receive care based on the existing standard of care, as outlined in the Rib Fracture Management Guideline (Appendix A). While it is conceivable that as few as 20 randomized subjects might be sufficient to show statistically significantly decreased opioid analgesic use (Primary Endpoint), it is anticipated that the full cohort of 50 randomized subjects would be desirable to examine the important secondary endpoints relating to resource utilization (hospital and ICU LOS), as well as to better understand the how ketamine improved care. Discontinuation of the study would be considered if greater than 33% of participants suffer adverse events felt to be related to the study drug.

5 SAFETY MANAGEMENT

5.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study and recorded as a secondary study outcome. If concern for adverse events related to study medication administration, providers will manage as if receiving low-dose ketamine infusion. Discontinuation of study drug will be at provider discretion.

5.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) they will be reported to the IRB in accordance with NMHH guidelines. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

Jouguelet-Lacoste et al. (2015) reviewed five meta-analyses and 39 clinical trials from 1996 to 2013 in which over 1400 patients received low-dose IV ketamine for pain control. No major complications, related to ketamine administration, were reported in this analysis[6].

STUDY ADMINISTRATION

5.3 Treatment Assignment Methods

5.3.1 Randomization

A randomization schedule (see Appendix B for sample) will be created using Microsoft Excel. The sample randomization schedule includes fictitious names and MR#s. Note: once the schedule is created. In a final document Column C would be hidden and probably Columns A-D would be "locked" (Protected), so that they could not be modified (values in Column D would change, but the formula to create those values could not be changed in a Protected document).

The randomization schedule will be generated (with appropriate instructions) in the pharmacy, who will also be responsible for maintaining and protecting the list, as subjects are enrolled. Neither the PI, Co-investigators, physicians, nurses, or others caring for the patient will be aware of whether or not a given patient is receiving ketamine or placebo infusion.

Once a patient agrees to participate in the study, a licensed physician, nurse practitioner, or physician assistant will enter an order for Rib Fracture Study Drug in the EPIC electronic record. That caregiver is responsible for insuring that the subject has consented to participate in the study and that a signed consent form resides in the subject's medical record. Prior to commencing infusion of the any study drug, the nursing staff will also confirm that a signed consent for the subject is present in the patient's medical record.

5.3.2 Blinding

During the duration of the study, the pharmacy personnel will be the only individuals who will have knowledge of study drug assignment. At the completion of the study (enrollment of 50 subjects) this information will be turned over to the study investigators. Under no circumstances should be drug allocation be released to any individuals prior to completion of the study.

5.3.3 Unblinding

Since ketamine is an approved medication, this is no specific reason for any caregiver to reasonably request that an individual's study drug allocation be unblinded. However, it is entirely reasonable that any and all caregivers should consider that all patients enrolled in the study are receiving ketamine and to use that information to make clinical decisions. If a caregiver is concerned that any aspect of a patient's condition, responses to treatment, etc. might be adversely impacted by possible administration of ketamine, then that clinician may discontinue the study drug at any time.

5.4 Data Collection and Management

Data will be extracted from patient records as contained in EPIC electronic health record.

5.5 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy. The Investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

5.5.1 Risk Assessment

Risks are not greater than minimal as discussed above in Section 5.2. Patients will be monitored as previously discussed in Section 3.7 according to Ketamine, Low Dose for Analgesia, Adult Order Set which is an approved NMHH Hospital Order Set.

The medication being studied is already approved for use as a pain medication adjunct at NMHH.

5.5.2 Potential Benefits of Trial Participation

Potential benefits of trial participation include the benefit to society as related to potentially convincing study results which may sway clinical practice in a manner that brings clinical benefit to those suffering from multiple rib fractures. Additionally, trial participants included in the experimental group may benefit from improved pain control related to the drug therapy.

5.5.3 Risk-Benefit Assessment

The risk of participation is related to the possible lack of ketamine infusion, in those that could benefit from its use, in the control group. There is also a very low risk of adverse

reaction to those receiving the medication in the experimental group. The benefit is enhanced pain relief those receiving the medication.

6 REFERENCES

1. Mowery, NT, et al. Practice management guidelines for management of hemothorax and occult pneumothorax. J Trauma. 2011;70:510-518.

2. Simon, BJ, et al. Pain management guidelines for blunt thoracic trauma. J Trauma. 2005;59:1256-1267.

3. Simon B, et al. Management of pulmonary contusions and flail chest: an eastern association for the surgery of trauma practice management guideline. J Trauma Acute Care Surg. 2012;73:S351-S361.

4. Galvagno SM, et al. Pain management for blunt thoracic trauma: A joint practice management guideline from the Eastern Association for the Surgery of Trauma and Trauma Anesthesiology Society. Journal of Trauma and Acute Care Surgery. 2016;81(5):936-951.

5. Zakine, J, et al. Postoperative ketamine administration decreases morphine consumption in major abdominal surgery: a prospective, randomized, double-blind, controlled study. Anesthesia and Analgesia. 2008;106: 1856-1861

6. Jouguelte-Lacost, J, et al. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. Pain Medicine. 2015;16:383-403.

7. Nesher, N, et al. Ketamine spares morphine consumption after transthoracic lung and heart surgery without adverse hemodynamic effects. Pharmocological Research. 2008;58:38-44.

8. Kugler, N, et al. Ketamine infusion for pain control in elderly patients with multiple rib fractures: Results of a randomized control trial. Journal of Trauma and Acute Care Surgery. 2019; 87(5): 1181-1188.

9. Carver, T, et al. Ketamine infusion for pain control in adult patients with multiple rib fractures: Results of a randomized control trial. Journal of Trauma and Acute Care Surgery. 2019; 86(2): 181-188.

Appendix A Rib Fracture Management Guideline

Purpose

The following guideline is intended to address and optimize pain management while monitoring pulmonary function in patients with multiple traumatic rib fractures with the goal of minimizing morbidity and mortality associated with blunt thoracic injury. A multidisciplinary clinical pathway in managing rib fractures has been shown to decrease associated infectious morbidity and mortality (Todd et al., 2006).

Definitions

Vital Capacity (VC): Maximum volume of air that a person can exhale after maximum inhalation.

Indication

In patients with multiple rib fractures, the following procedures will be implemented to minimize associated complications and optimize outcomes.

Procedures

1) The following patients should be considered for TNICU admission, related to diagnosis of rib fractures:
    a. Patients 65 years of age or older, with multiple rib fractures
    b. Patients with 4 or more rib fractures and/or flail segment
    c. At provider discretion.
2) Multimodal Analgesic Strategy
    a. Scheduled Acetaminophen - 1000 mg PO every 6 hours unless contraindicated
        i. **GERIATRIC DOSING:** Age ≥ 65 y/o - 1000 mg PO every **8 hrs** unless contraindicated
        ii. For intubated patients or inability to safely take PO:
            1. 650mg suppository every 6 hrs, or
            2. 1000 mg IV every 6 hours unless contraindicated
                a. **GERIATRIC DOSING:** Age ≥ 65 y/o - 1000 mg IV every **8 hrs** unless contraindicated
    b. Scheduled NSAID – Ibuprofen 600mg PO every 6 hours, or Ketorolac 15-30mg IV every 6 hours, unless contraindicated and for duration specified by attending provider
        i. **GERIATRIC DOSING:** Age ≥ 65 y/o – 400mg po every 6 hrs, or Ketorolac – 7.5-15mg IV every 6 hours, unless contraindicated and for duration specified by attending provider
    c. Lidoderm 5% patches (1-3) over and/or medial to fracture site(s)
    d. Narcotic analgesics

i. Initial treatment to include oxycodone – 5mg to 10mg po every 4hrs PRN mild to moderate pain; and hydromorphone – 0.4mg to 0.8mg IV every 2 hrs prn moderate to severe pain, with dosing adjusted for patient age and weight, unless contraindicated
ii. Age ≥ 65 y/o, opioid-naïve, and low body mass - oxycodone – 2.5mg to 5mg po every 4hrs prn mild to moderate pain; and hydromorphone – 0.2mg to 0.4mg IV every 2-4 hrs prn moderate to severe pain, unless contraindicated
iii. If pain inadequately controlled, based on patient report and provider assessment, with above analgesics, Patient Controlled Analgesia pump to be considered with appropriate dosing (per Adult Opioid Naïve or Tolerant PCA Orderset) and likely discontinuation of other narcotic analgesics based on provider assessment

e. Muscle relaxants – methocarbamol 500-1000mg PO every 6 hrs as needed or 500-1000mg IV every 8 hrs (not to exceed 3 day course), unless contraindicated and based on provider discretion
    i. **GERIATRIC DOSING:** methocarbamol 500mg PO every 6 hrs as needed
f. Ketamine infusion (per Ketamine, Low Dose for Analgesia orderset)– 0.1mg/kg/hr (5-20mg/hr) to be used as analgesic adjunct for poorly controlled pain or at provider discretion
g. Consider as needed: other pharmacologic modalities such as gabapentin and/or Vistaril (hydroxyzine) (Vistaril not recommended in geriatric population)
h. Anesthesiology consult for placement of epidural catheter is recommended for the following patients (contact at x13982, intubated patients may not be candidates, INR must be less than 1.3):
    i. patients ≥65 y/o with multiple rib fractures, and/or flail segment
    ii. patients ≥45 y/o with 4 or more rib fractures, and/or flail segment
    iii. at provider discretion
i. Non-pharmacologic treatments
    i. Splinting education/implementation per Nursing
    ii. Ice (cold pack) therapy
    iii. Positioning/activity (see below)

3) Multidisciplinary Orders
    a. Respiratory Therapy
        i. EZ-PAP- three times daily if failing to meet IS goal, if increasing oxygen demands from baseline, or at provider discretion. Contraindicated if untreated pneumothorax is present. Chest XR may need to be ordered prior to initiation of therapy.

ii. Consider Pulmonary function testing, via RT consultation, specifically Forced Vital Capacity (FVC), if evidence of failure to progress or worsening IS volumes
    1. FVC values < 1L should be communicated by RT staff to Trauma Service Provider for consideration of escalation of respiratory interventions and/or TNICU admission

b. Physical Therapy consult – evaluate and treat with emphasis on early mobilization
c. Nursing
    i. Daily ambulation (as allowed by weight-bearing status, activity orders, and/or clinical status)
    ii. Up in chair multiple times daily and for meals (as allowed by weight-bearing status, activity orders, and/or clinical status)
    iii. Incentive Spirometry (IS) – Ten or more times every hour while awake with ongoing monitoring and coaching by RN. Goal of >15mL/kg volumes written on communication board. If patient failing to meet IS goal, Trauma Provider to be notified. Incentive Spirometry volumes obtained and frequency to be recorded in System Assessment Pulmonary flowsheet

4) Repeat imaging
    a. Repeat chest x-ray and/or CT chest should be completed if concern for worsening pulmonary function and/or at provider discretion
5) Surgical intervention
    a. Rib fixation should be considered in the following patients:
        i. 3 or more displaced rib fractures
        ii. Flail chest
        iii. Failure of medical management
        iv. Severe chest wall deformity

Appendix B Sample Randomization Schedule

Subject #	Drug	Rand#	Subject Infusion Rate (mL/hr)	Subject Weight (Kg)	Subject Name (Last, First)	Subject MR#
1	Ketamine	0.0075	7	70	Smith, John	1234567
2	Ketamine	0.01395	6.5	65	Nelson, Sophia	2345678
3	Saline	0.03597	8.1	81	North, Katrina	9876542
4	Saline	0.05186	7.85	78.5	Campbell, Robert	56789123
5	Ketamine	0.06602	6.73	67.3	Mueller, Thomas	432189
6	Saline	0.06938	0			
7	Ketamine	0.10318	0			
8	Ketamine	0.11022	0			
9	Ketamine	0.13401	0			
10	Saline	0.13672	0			
11	Ketamine	0.1671	0			
12	Saline	0.18297	0			
13	Ketamine	0.25649	0			
14	Ketamine	0.25992	0			
15	Ketamine	0.26027	0			
16	Saline	0.31793	0			
17	Ketamine	0.3418	0			
18	Saline	0.35012	0			
19	Saline	0.3554	0			
20	Ketamine	0.40807	0			
21	Saline	0.40814	0			
22	Saline	0.41905	0			
23	Saline	0.4319	0			
24	Saline	0.44334	0			
25	Saline	0.45316	0			
26	Ketamine	0.48629	0			
27	Saline	0.53763	0			
28	Saline	0.54659	0			
29	Ketamine	0.55659	0			
30	Ketamine	0.5639	0			
31	Ketamine	0.5734	0			
32	Ketamine	0.57587	0			
33	Saline	0.58346	0			
34	Ketamine	0.60677	0			

Subject #	Drug	Rand#	Subject Infusion Rate (mL/hr)	Subject Weight (Kg)	Subject Name (Last, First)	Subject MR#
35	Ketamine	0.61165	0			
36	Saline	0.61363	0			
37	Ketamine	0.66886	0			
38	Saline	0.67536	0			
39	Ketamine	0.7464	0			
40	Saline	0.75254	0			
41	Saline	0.8133	0			
42	Saline	0.81479	0			
43	Saline	0.8249	0			
44	Ketamine	0.83454	0			
45	Saline	0.85056	0			
46	Ketamine	0.88193	0			
47	Ketamine	0.90319	0			
48	Ketamine	0.93575	0			
49	Saline	0.93703	0			
50	Saline	0.98351	0			