



INSTITUTIONAL REVIEW BOARD
SCIENTIFIC CONSULTANT CHECKLIST

Date:	Thursday, 06/03/2021	Date Review Due to HRP/IRB:	Thursday, 06/24/2021
HS# 2021-6525			
Study Title: Dexmedetomidine for Acute Pain Control in Patients with Multiple Rib Fractures: A Randomized Controlled Trial			
Lead Researcher: Jeffry Nahmias			
Department: Division of Trauma, Burns, Surgical Critical Care and Acute Care Surgery			

Hypothesis/Specific Aims/Research Variables	
1. Are the hypotheses clearly identified in the protocol narrative?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Comments: We hypothesize that the addition of dexmedetomidine (precdex) to a multimodal pain regimen will decrease numerical pain scores (NPS) and opioid use in blunt trauma patients with 3 or more rib fractures.	
2. Are the specific aims (purpose) of the research justified by the hypotheses?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Comments: The aim of this study is to evaluate the effectiveness of adding a dexmedetomidine (precdex) infusion to a multimodal pain regimen to treat multiple rib fractures.	
3. Are the primary outcome variable(s), secondary outcome variables, and predictors and/or comparison groups adequately described and appropriate based upon the hypotheses and aims?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Comments: <u>Primary outcomes:</u> objective numerical pain scores (NPS) and oral morphine equivalent (OME) utilization <u>Secondary Outcomes:</u> Epidural use, incentive spirometry (IS), ICU LOS, Hospital LOS, Pulmonary complications (PNA, intubation), mortality, delirium, and adverse events	

Methodology/Study Design	
4. Is the methodology and study design appropriate to assess the hypotheses and the aims?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Comments:	

This is a prospective, randomized, double-blinded, placebo-controlled trial. Patients will be identified as they present to the trauma bay and meet eligibility criteria. Following informed consent patients will be randomized to either the intervention or control arm. Randomization and allocation concealment will be managed by a nominated independent individual(s) not involved in patient care or data extraction/analysis. The consenting physician will contact the randomization individual by phone. They will use a random number generator to assign group in a 1:1 ratio and then maintain a password protected randomization database that is only accessible to the principal investigator and randomization individual(s).

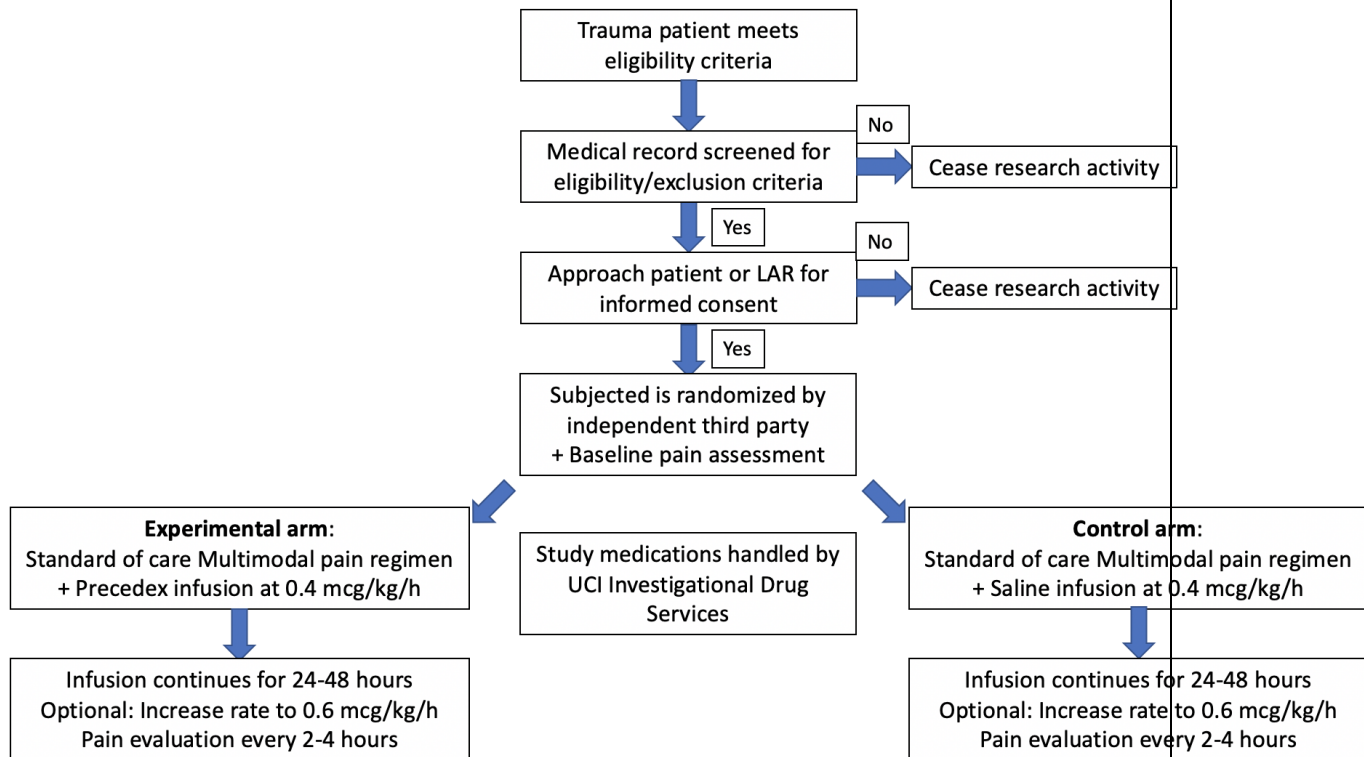
The intervention arm will receive an infusion of dexmedetomidine (precdex) at 0.4-0.6 mcg/kg/h (Based off ideal body weight). The control arm will receive an infusion of normal saline. Medication distribution and management will be handled by the Investigational Drug Service (IDS) at UCI medical center. A pharmacist who does not participate in the rest of the study will encode the study drug accordingly. Dexmedetomidine is approved for ICU and procedural sedation, and its use in this study for analgesic is off-label. A base line pain assessment will be performed using a numerical pain score (NPS). Infusions will start within 12 hours of arrival to the ICU and will continue for 24 hours. Infusion will stop once the patient is transferred out of the ICU or at 24 hours, whichever is first. In the scenario of possible adverse events (as listed below) the physician can hold or stop the study medication at their discretion. All enrolled patients will also receive a multimodal pain regimen with acetaminophen, NSAIDs, lidocaine patch, gabapentin, and muscle relaxants. For moderate and severe pain (5-10) patients will receive 5-10mg oxycodone every 4-6 hours upon request. Nursing staff will assess pain per the unit standard of care. NPS and opiate administration will be documented in the EMR by the nursing staff. All participants, providers, and staff will be blinded unless medical necessity requires patients to be unblinded.

Data will be collected prospectively from the EMR by blinded researchers and entered into a REDCap database. Data collection will include demographics, mechanism of injury, injury severity score (ISS), imaging, pain scores, pain medications, incentive spirometry, pulmonary complications, ICU LOS, hospital LOS, discharge disposition, and any other clinically relevant data.

1. Patient identification and consenting – The research staff will identify patients that meet eligibility criteria and screen their medical record for inclusion. Their mental status, capacity, and physical status will be assessed. If they meet criteria the patient or their LAR will be approached for informed consent
2. Randomization – patients will be randomized independently by a third party not involved in patient care or data extraction. Researchers and care providers will be blinded to which arm they are in for the duration of the trial.
3. Baseline assessment of pain
4. Treatment/Study medication - Infusion of either dexmedetomidine (precdex) or normal saline – administration of study medication will be handled/monitored by the IDS pharmacy. Starting infusion will be set at 0.4 mcg/kg/h. Infusion will continue for 24 hours. If pain is uncontrolled (NPS>5) after 2 consecutive evaluations patients/care providers will have the option to increase infusion to 0.6 mcg/kg/h.
 - All patients will receive standard of care pain medications with acetaminophen, NSAIDs, lidocaine patch, and muscle relaxants. Unless there are contraindications.
 - Nursing staff will document pain scores per unit policy every 2-4 hours
 - Opiates will be offered every 4-6 hours for severe pain (NPS>7)
5. Treatment ends – infusions will stop after 24 hours or when the patient is transferred out

of the ICU

6. Data extraction – data will be collected prospectively by our blinded researchers and entered into a REDCap database



5. Are the stratification, randomization, and blinding scheme procedures appropriate?

☒ Yes ☐ No ☐ N/A

Comments:

6. Are the study endpoints and criteria for evaluation justified?

☒ Yes ☐ No

Comments:

Primary end points:

1. Numerical pain score (NPS) – subjective assessment of patient's pain on a scale of 0-10 which is assessed and recorded by our nursing staff as part of standard of care and before any pain intervention. We will calculate as area under the curve for pain trajectory.

2. Oral morphine equivalents (OME) – measured at 24 and 48 hours

Secondary endpoints:

Epidural use – patients that fail pain management will be offered an epidural

ICU length of stay – number of days in the ICU

Hospital length of stay – number of days admitted to the acute care hospital

Respiratory complications – includes events such as unplanned intubation, pneumonia, pneumothorax

Incentive spirometry (IS) – measured in ml and assessed by nursing per unit policy
Mortality – in-hospital mortality rate and 30-day mortality
Incidence of delirium – CAM-ICU score at 24 and 48 hours
Adverse events – rate of dtv, pe, cardiac events, infections, ICU re-admission, unplanned operation, etc
Adverse events related to dexmedetomidine - Hypotension (SBP <90), Bradycardia (HR <55),

Additional Hospital information collected – includes but not limited to

Medical history and co-morbidities

Demographics

Initial trauma assessment and evaluation – injuries, Injury severity score, GCS, vitals, weight, and height

Laboratory results – CBC, BMP, LFTs, PT/PTT, cultures

Imaging results – x-rays, ultrasounds, and CT scans

Statistical Considerations

7. Are the statistical method(s) appropriate for the stated specific aims and hypotheses?

☒ Yes ☐ No

Comments:

The UCI Institute for Clinical and Translational Science Descriptive (ICTS) will be assisting with power analysis and final data analysis. All descriptive statistics (mean \pm SD, median with IQR, or count with percentage) will be calculated for all demographic, clinical variables, medical interventions, and outcomes. Any associations between each continuous, binary, or categorical variables will be examined using a student t-test, Mann-Whitney U test, Pearson's χ^2 , or Fisher's exact t-test.

Primary outcomes will be compared using chi-square or T-test

Secondary outcomes (including differences in patient demographics) will be analyzed using a combination of t-test and chi-square where appropriate.

8. Is the power / sample size appropriately justified?

☒ Yes ☐ No ☐ N/A

Comments:

N=40

A significant reduction in NPS is defined as a 2-point reduction on a 0-10 scale. Based on prior patient pain data, for our target population, the between patient mean was 6.18 with a standard deviation of 2.01. Based off this assumption, our sample size was calculated at approximately 17 patients per group for an 80% power at an alpha of 0.05. We plan to enroll 20 patients in each arm and to account for dropout rate, we set out to screen/consent 60 patients. We plan to perform an interval analysis after one year to reassess sample size.

SUMMARY

Summarize the scientific concerns to be addressed by the Lead Researcher (LR). *(These comments will be incorporated into the IRB memo sent to the Lead Researcher):*

The investigators have provided adequate responses to the first statistical review therefore the statistical merit of this study is now acceptable.

Study design

- Pain treatment is tailored according to patient's trauma severity. Even with randomization, the distribution of patients with more severe trauma could be uneven between the two study arms just by random chance due to the small sample size of patients. Would it be possible to consider block randomization in which patients are paired by similar trauma severity before they are randomized into experimental versus control arms? Block randomization would ensure that patients are equally distributed between the two arms by their trauma severity.
- **Responses:** Thank you for the comment by the SRC, we agree that trauma severity is a potential confounder on pain. Most often, injury severity is estimated by the injury severity score (ISS). However, we are unable to obtain the ISS until many days after admission and thus would not be able to perform a block randomization. Furthermore, we have reviewed the literature and a similarly designed RCT on Ketamine had two groups with similar ISS just from normal randomization (Kugler 2019). To account for this concern, we would plan to add a sub-group analysis of ISS>15 and a separate analysis of ISS<15.
- Added to the protocol narrative is the planned subgroup analysis

Statistical methods

- The primary outcome is the numeric pain score documented every 2 hours during the 24 hours of pain treatment. The investigators stated that they will 'calculate the area under the pain trajectory' for each patient. Please describe in detail how 'the area under the pain trajectory' is adjusted for a patient's baseline pain and how 'the area under the pain trajectory' is calculated when opioid is given to a patient.
- **Responses:** All NPS data will be collected by the nursing staff and recorded through the patient's electronic medical record. Each patient's encounter will be organized chronologically by time of pain score entry. We will denote time zero as the first pain score after initiation of the study medication. Each additional pain score will be recorded as the time elapsed since time zero, until the pre-determined 24-hour cut-off. A 24-hour observation window was determined based off two reasons. One, we are interested in studying the acute pain period immediately after admission. Second, dexmedetomidine is only FDA approved for up to 24 hours of continuous use. The area under the pain trajectory curve will be calculated using the trapezoid rule with linear interpolation between time points. Giving us a time-weighted average of pain scores.
- To account for baseline pain or medications received before time zero, we will record all documented NPS and medications received prior to the start of the study mediation (time zero). The baseline pain score will be calculated by the average NPS prior to time zero. In addition to total pain, we will record the total reduction in pain from baseline every 2 hours.
- Perceived pain is a complex process, which is why a multimodal pain regimen is implemented. All patients will receive Gabapentin, Tylenol, lidocaine patches, and muscle relaxers. Additionally, opioids are offered for NPS >5. Pain medications of different mechanisms work in synergy, and we do not believe opioids will nullify the effect of dexmedetomidine. Since both groups are receiving opioids and we will be collecting opioid equivalent data we feel this would be sufficient to evaluate opioid use as adjusting for timing would be difficult and

furthermore this was not done in a recent randomized controlled trial on this topic related to use of ketamine (Kugler 2019).

- Our protocol narrative has been updated to reflect the above changes

RECOMMENDATION

- ☒ **SCIENTIFIC MERIT OF THE STUDY IS ACCEPTABLE** (No revisions are necessary prior to IRB review.)
- ☐ **MINOR CHANGES REQUIRED, READY FOR IRB REVIEW** (Study requires minor revisions to adequately justify the scientific merit of the study. Recommend that the LR address these revisions).
- ☐ **SUBMISSION INCOMPLETE AND/OR SIGNIFICANT DEFICIENCIES NOTED ABOVE - NOT READY FOR IRB REVIEW** (Study requires significant revisions and/or has major deficiencies. Revisions to documentation required to adequately address the scientific merit of the study. Revisions should be re-reviewed by Scientific Consultant prior to IRB review. Strongly recommend LR seek methodological/statistical consultation.)

TUYEN HOANG, PhD

Scientific Consultant's signature

6/16/2021

Date

*If submitted electronically, you may type your name in space above in substitution of hand signature