A Prospective Comparison of Continuous Intravenous Lidocaine Infusion Versus Placebo for Rib Fracture Analgesia

Study Protocol and Statistical Analysis Plan

NCT04140396

October 22, 2019

Title
Continuous intravenous lidocaine infusion versus placebo for rib fracture analgesia

Study personnel
Lei Xu MD, Shruthi Basireddy, Ban Tsui MD (PI)

Institutional funding
None

Additional sources of funding
None

Background & Preliminary Unpublished Data

Thoracic traumas comprise 10-15% of all major traumas. The most common mechanism is blunt injury and the majority involves rib fractures. In fact, rib fractures are identified in 10-40% of trauma patients and they are associated with significant morbidity, mortality, and long-term disability (1). The majority of the morbidity stems from pulmonary complications such as ARDS, pneumonia, aspiration, empyema, etc. (2). Studies have examined the multitude of factors that influence mortality after traumatic rib fractures and they include number of rib fractures, pre-existing cardiopulmonary disease, increased age, and associated level of pain (3). Thus the cornerstones of clinical management for rib fractures centers on pulmonary hygiene and adequate analgesia.

The current cornerstone of pain control for rib fractures is oral and intravenous opioids, especially in the form of patient-controlled analgesia (IV PCA). Opioids however are associated with multiple adverse effects including sedation, respiratory depression, cough suppression, and increased risk of delirium. In patients with multiple rib fractures, advanced age, or severe and difficult to control pain – systemic analgesia with opioids is often not sufficient and in these scenarios thoracic epidural anesthesia (TEA) has been the gold standard. Retrospective studies however have not shown significantly improved clinical outcomes in rib fracture patients who received TEA. One retrospective study by Yeh (4) compared outcomes in 187 patients admitted with rib fractures and noted no significant difference in the incidence of pulmonary complications between patients who received TEA versus those who did not. However patients who received TEA had a significantly longer hospital and ICU length of stay., Thoracic epidural anesthesia is also technically challenging and associated with unwanted side effects particularly hypotension, urinary retention, and unintentional motor blockade (5). In addition TEA is contraindicated in several situations (such as head trauma, spinal cord injury, anticoagulation, hemodynamic instability) and carries significant, albeit rare, complications (epidural hematoma etc).

In the past few decades, intravenous lidocaine infusion (IVL) has emerged as a new tool in the arsenal of multimodal analgesia. Multiple randomized clinical trials have been performed analyzing the analgesic effects of intravenous lidocaine infusion and few adverse events have been reported, demonstrating that it is overall well tolerated. Furthermore studies have shown other beneficial effects of IVL such as it's anti-inflammatory properties. In vitro studies of white blood cells incubated with lidocaine demonstrated decreased release of different cytokines such as leukotriene B4 (potent stimulation of neutrophil activity) and interleukin-1alpha. Furthermore, in animal models of hyperoxia-induced lung injury, intravenous lidocaine infusion decreased

chemotactic/cytokine factors in bronchoalveolar lavage fluid and resulted in less neutrophil accumulation compared to placebo. (6).

At our institution SHC, both IVL and TEA have been used as part of a regimen of multimodal analgesia for pain in rib fracture patients for which opioids fail to reduce pain scores to <=4 or have poor respiratory effort. A retrospective analysis performed by our colleagues at Stanford University in comparing patients who received IVL versus TEA demonstrated that there were no significant differences in pain scores (at 24 and 48hrs), hospital LOS, incentive spirometry volumes, or pulmonary complications (7). This retrospective analysis however is confounded by biases including the fact that patients considered for TEA are generally higher risk for complications. To this date, there have been no published randomized clinical trials (RCT) evaluating the effectiveness of IVL in management of traumatic rib fracture pain. We thus propose a novel RCT comparing treatment with IVL versus placebo in patients admitted for traumatic rib fractures in order to evaluate the clinical effectiveness of IVL on OME consumption, pain scores, incentive spirometry volumes, cough strength, and LOS.

Hypothesis

We hypothesize that continuous intravenous lidocaine infusion will provide improved pain control as demonstrated by decreased OME consumption at 24 and 48 hours compared to placebo in adult patients with acute traumatic rib fractures.

Methods

This study will include all adult patients admitted to Stanford Health Care with two or more acute traumatic rib fractures. This study will exclude patients with hemodynamically instability, mechanical ventilation, polytrauma (defined as bone or organ injury outside the thorax), pregnancy, incarceration, local anesthetic allergy or contraindications to lidocaine (Stokes-Adams syndrome, Wolff-Parkinson-White syndrome, or severe degrees of sinoatrial, atrioventricular, or intraventricular block) and chronic opioid use.

All study patients will be started on the standard of care multimodal regimen at SHC being currently used by the trauma surgery admitting team for all adult patients admitted with rib fractures. This consists of: Acetaminophen 1g TID, opioid prn (PO oxycodone and IV hydromorphone), Celebrex 100mg PO BID (for those without contraindications), gabapentin 100mg qHS (increased as tolerated to max 300mg PO q8h) and any baseline chronic outpatient analgesics. Patients will receive either a lidocaine infusion or a placebo infusion consisting of normal saline at 10mL/hour. All patients on study drug (IVL) will have lidocaine levels drawn q8h. In addition, all patients will have blood drawn for a panel of inflammatory biomarkers right before intervention initiation, at 24hours and at 48 hours. Patients, will be blinded to the treatment however nurses, treating clinicians, and research personnel will not as they will monitor lidocaine serum levels and adjust infusion doses accordingly.

Patients will be systematically evaluated at 12-24 hours after initiation of the intervention for failure (defined as pain scores at rest of > 7, clinically significant side effects from opioids, or ICV of <=500cc with appropriate effort). For the patients on placebo arm who have “failed” - they will cross over to the IVL treatment arm. For patients on the treatment IVL arm who have “failed” – their lidocaine level will first be checked. If it is subtherapeutic, the lidocaine infusion dose will be increased to achieve a therapeutic lidocaine level. If the lidocaine level is withinin the therapeutic window – these patients will get removed from the study and receive a consult to

the Acute Pain Services for further pain management. Any patient who has clinically significant side effects of IVL will have the infusion stopped and be removed from the study.

An IRB approval will be obtained and all patients will be randomized to either the placebo arm (control) or the intervention arm (IVL) within 16 hours of hospital admission.

Data analysis and sample size calculation

The primary end point for this study is oral morephine equivalents (OME) consumption at 24 hours of treatment. Secondary end points include OME at 48 hrs, pain scores at rest and with cough and deep inspiration, incentive spirometry volumes, PIC score, length of hospital stay, inflammatory biomarkers, and rates of pulmonary complications (including need for positive pressure ventilation, pneumonia, aspiration, supplemental oxygen). The PIC score will be calculated according to Figure 1 (See below). Pain will be scored on a Numeric Rating Scale (NRS) of 0-10, where 0 is no pain and 10 is the worst imaginable pain. There will also be subgroup analyses by geriatric status and >4 rib fractures.

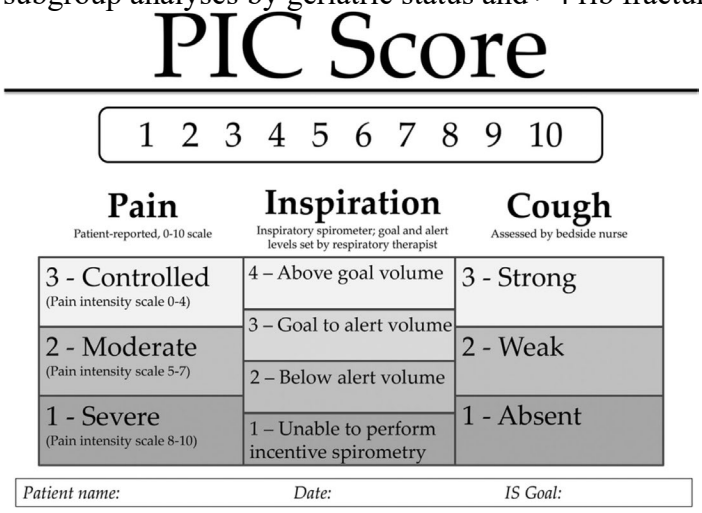

Figure 1: PIC score as described by Witt and Bulger (8). PIC is a composite score comprising pain level, ICV, and cough strength.

At our institution, preliminary retrospective data (unpublished) shows that continuous IV lidocaine infusion reduces OME consumption from average of 174 OME/24hr with standard deviation 190 OME/24hr (extrapolated from OME consumption during time period prior to initiation of IVL) to 85 OME/24hr with standard deviation of 68 OME/24hr. Since we do not have data on patients that were not treated with IVL, we assume that this clinically significant difference would not occur in the placebo group. Therefore, with a type 1 error rate of 0.05 and power of 80%, sample size estimation suggests 144 patients total – 72 per group, would be required to demonstrate significance. To compensate for dropouts and incomplete data, 80 patients per group will be targeted for enrollment.

In terms of statistical analysis, we plan to use the Mann-Whitney U test for all continuous, ordinal, and interval variables, to determine equality of means between two groups regardless of normality. We will use two-sided P values of < 0.05 as the cutoff for statistical significance. We will collaborate with a statistician to perform further in-depth analyses especially for the subgroup analyses.

Intervention

All adult patients admitted to SHC for acute traumatic rib fractures will have their MRN and last name paged to the research team upon admission by the treating physician team (trauma surgery). The trauma surgery team will discuss with the patient that there is a research study about pain management in patients with rib fractures and obtain permission for the research study team to contact the patient. Furthermore, the primary service (trauma surgery) will put all patients on the standard baseline multimodal regimen as described above.

Potential study patients will have their charts reviewed and if deemed to fit the inclusion/exclusion criteria, the patient will be evaluated for informed consent by the research team within 16 hours of admission. If the patient provides consent, he or she will be immediately randomized to either the control arm (normal saline infusion) or the intervention arm (continuous intravenous lidocaine infusion initially at 1.0mg/kg/hr, also referred to as 'study drug'). Patients will be blinded to the treatment. Patients on study drug (IVL) will have q8h lidocaine serum levels drawn. Treating clinicians will monitor serum lidocaine levels and adjust infusion dose with pharmacy.

The length of study drug or placebo infusion will be approximately 72 hours and thus the study period (defined as the period of active participation by the study participant) will be approximately 3 days. At conclusion of the study period, the patient will no longer need to be blinded to treatment. At the conclusion of the study period it is up to the treating clinician to continue the intravenous lidocaine infusion if the patient is on the study drug arm.

There will be no other changes to the trauma rib fracture protocol.

The following describes the points of data collection:

- Pain scores at rest will be collected by RNs via a Numeric Rating Scale as per SHC hospital inpatient ward protocol every 4 hours and upon arrival (NRS, 0-10, where 0 is no pain and 10 is the worst imaginable pain).
- In addition to the pain scores pre-randomization, time 0 will be designated as prior to starting either the control or intervention treatment.
- The research team will assess all patients for: NRS pain scores at rest/deep inspiration/deep cough, maximum ICV (of 3 attempts), cough strength, signs/symptoms of lidocaine toxicity. These measurements will be taken at time 0 and then daily up through day 3 of the study period.
- Serum lidocaine levels will be drawn q8h for all patients on the study drug as per SHC protocol.
- All patients will also get blood drawn for panel of inflammatory biomarkers at time 0, 24 hours, and 48 hours.
- Analgesic consumption will be recorded in the following increments (pre-intervention to time 0, time 0-24hr, 24-48hr, and 48-72hrs).
- Electronic medical records will be analyzed for: demographic data, name, age, MRN, gender, weight, height, medical history, medication history, current medical conditions/diagnoses and medications while hospitalized, medical complications from rib fractures.

Data safety monitoring plan

Please see the "Methods" and "Intervention" sections for the summary of the protocol for this prospective study. No children or pregnant women will be enrolled in the study per inclusion/exclusion criteria as previously described. Patients who experience significant pain despite the described multimodal analgesic regimen and intervention will be removed from the study and considered for alternative treatments (such as thoracic epidural, etc) and acute pain service consult. Treating clinicians and research personnel will not be blinded to assignment. All patients on the study drug will have serum lidocaine levels monitored by treating clinicians. Furthermore, research personnel will assess for symptoms of lidocaine toxicity daily (in addition to clinician and RN assessments). Treating clinicians will work with pharmacy to adjust lidocaine infusion based on lidocaine levels (as per SHC protocol) and if a patient has signs of lidocaine toxicity, he/she will be considered for removal from the study immediately.

This project is a multidisciplinary collaboration between the Anesthesiology and Surgery departments. The study personnel include the PI - Dr. Ban Tsui, a professor in the Department of Anesthesiology at Stanford University, the study primary investigator - Dr. Lei Xu, a regional anesthesiology fellow, and the clinical research coordinator Shruthi Basireddy. The collaborators included, Dr. Kristen Lea Staudmayer (Trauma lead), Assocate Professor, Department of General Surgery, and Einar Ottestad (Acute Pain lead), Clinical associate professor, Department of Anesthesiology. All study personnel will be monitoring this study throughout the collection of data for all patients enrolled. This includes ensuring the study is conducted according to the protocol, monitoring enrollment, collecting data in a confidential manner on password protected and encrypted software, and reporting adverse events promptly to the IRB and any other applicable agencies. We will be applying our GCP training to conduct this study and providing updates to the IRB as appropriate per guidelines.

Significance

The foundation of clinical management for rib fractures centers on pulmonary hygiene and adequate analgesia. The current mainstay of pain control for rib fractures across the United States is oral and intravenous opioids. Opioids however are associated with multiple adverse effects including sedation, respiratory depression, cough suppression, and increased risk of delirium. Furthermore, in patients with multiple rib fractures, advanced age, or severe and difficult to control pain – systemic analgesia with opioids is often not sufficient and in these scenarios thoracic epidural anesthesia (TEA) has been the gold standard. Epidurals however are invasive, have side effects (such as hypotension and urinary retention), and carry risk of serious complications (epidural hematoma, etc). Intravenous lidocaine infusions are an alternative non-opioid and noninvasive method to reduce pain, and the retrospective study done by our colleagues at SHC (7) would suggest IVL to be similar to thoracic epidural in terms of decreasing pain from acute rib fractures. Retrospective studies however have inherent confounding factors and thus we are proposing this novel randomized clinical trial. This trial has the potential to not only demonstrate and measure the effectiveness of IVL in treating rib fracture pain, but if clinically significant results are found, it has the potential to change clinical practice across the United States.

References

1. Flagel BT, Luchette FA, Reed RL, Esposito TJ, Davis KA, Santaniello JM, Gamelli RL. Half-a-dozen ribs: the breakpoint for mortality. Surgery. 2005 Oct;138(4):717-23; discussion 723-5.
2. Gordy S, Fabricant L, Ham B, Mullins R, Mayberry J. The contribution of rib fractures to chronic pain and disability. Am J Surg. 2014 May;207(5):659-62; discussion 662-3.
3. Battle CE, Hutchings H, Evans PA. Risk factors that predict mortality in patients with blunt chest wall trauma: a systematic review and meta-analysis. Injury. 2012 Jan;43(1):8-17.
4. Yeh DD, Kutcher ME, Knudson MM, Tang JF. Epidural analgesia for blunt thoracic injury--which patients benefit most? Injury. 2012 Oct;43(10):1667-71. doi: 10.1016/j.injury.2012.05.022. .
5. Malekpour M, Hashmi A, Dove J, Torres D, Wild J. Analgesic Choice in Management of Rib Fractures: Paravertebral Block or Epidural Analgesia? Anesth Analg. 2017 Jun;124(6):1906-1911.
6. Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: a new therapeutic indication? Anesthesiology. 2000 Sep;93(3):858-75.
7. Aggarwal A. A Role for Peripheral Intravenous Lidocaine Infusion for Rib Fracture Pain Management. Poster presented at: ASRA 16th Annual Pain Medicine Meeting of the Society of Regional Anesthesia and Pain Medicine; Nov 16-18, 2017; Lake Buena Vista, FL.
8. Witt CE, Bulger EM. Comprehensive approach to the management of the patient with multiple rib fractures: a review and introduction of a bundled rib fracture management protocol. Trauma Surg Acute Care Open. 2017 Jan 5;2(1):e000064.