Clinical Protocol

E-PERC: *Early Percutaneous Cryoablation for Pain Control after Rib Fractures for Elderly Patients*

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Investigator: Dr. Joseph Forester

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Early Percutaneous Cryoablation for Pain Control after Rib Fractures for Elderly Patients (E-PERC)

Trauma team: Ya-Chen Lee MS, ACNP-BC; Rachelle Rosales BSN, RN, PCCN; Kris Gallegos RN TCRN; Michelle Woodfall MS RN CEN CCRN; ; David A Spain MD; *Joseph D Forrester MD MSc* (Principle Investigator)

Interventional Radiology: Nishita Kothary MD

Study Coordination Team: Sydney Guthrie-Baker, Alexandra Myers, Anisha Abreo
Biostatistician: Michelle Earley

Background:

Rib fractures are common injuries sustained after trauma[1–3] – in 2017, nearly 500,000 emergency department visits in the United States involved a patient with rib fractures[4]. In addition to causing morbidity and mortality in injured patients[2], rib fractures have been associated with chronic pain and prolonged disability[5–7]. The prevalence of adverse outcomes associated with rib fractures rises with age starting as early as the fifth decade of life[8] and increases significantly in patients over 65 [9–12]. A number of institutions[13–15], including our own[16], have implemented evidence-based, multidisciplinary care pathways to improve clinical outcomes in patients with rib fractures. These care pathways may be particularly beneficial to elderly patients. Tignanelli *et al.*[17] recently reviewed the treatment of over 625,000 rib fracture patients in 777 US trauma centers and found that surgical stabilization of rib fractures (SSRF), intensive care unit (ICU) admission of patients over 65 years old, and neuraxial blockade in patients over 65 resulted in decreased mortality.

SSRF requires open reduction and fixation of rib fractures to restore anatomic alignment of fracture fragments in order to decrease pain and restore respiratory mechanics[15]. Current consensus guidelines[18] recommend SSRF in patients with physiologic flail chest and multiple rib fractures with bi-cortical displacement, but do not address management of elderly patients specifically. Zhu *et al.*[19] conducted a propensity matched retrospective study of 758 patients over age 65 who presented with rib multiple fractures and found a statistically significant reduction in mortality among elderly patients who underwent SSRF. While these findings suggest SSRF may be beneficial in geriatric populations, this remains a higher risk surgical population. Frailty, defined as a decrease in physiologic reserves[20], is common among persons ≥65 years and a known correlate of worse surgical outcomes in this population[21]. Taken together, these findings suggest that SSRF may not be the treatment of choice for all geriatric patients.

In addition to the risks associated with surgery, there are inadequacies associated with the non-surgical components of existing rib fracture care pathways. Pain medications can be problematic as adequate analgesia must be balanced with the risks of over-sedation and respiratory depression with gabapentin and narcotics. Non-steroidal anti-inflammatory drugs can exacerbate underlying renal dysfunction. Neuraxial[24] and regional anesthesia[25] blocks are effective but technically demanding and relatively short-lived. ICU admission exposes frail, elderly patients to deleriogenic environments[26] and ICU-associated pathogens. There is, therefore, a *critical need* for durable, long-term pain control for elderly patients with rib fractures that are unable to undergo surgical fixation in order to minimize their risk of complication and return to baseline functional capacity as soon as possible.

Cryoablation of intercostal nerves offers a minimally invasive method to deliver long term pain control. Direct application of cold to nerves destroys nerve axons, resulting in Wallerian degeneration of the distal nerve without distorting epineurial or perineurial tissue. Preservation of peri- and epineurium provides a scaffold for peripheral nerve regeneration which provides reversible anesthesia lasting months[27]. Cryoablation of intercostal nerves under direct visualization has been validated for long-term analgesia after video assisted thoracoscopic surgery (VATS) for pectus excavatum in children reducing procedural pain and length of stay

[28,29]. More recently, case reports have explored use of VATS to perform intercostal nerve cryoablation as an anesthetic adjunct following SSRF[30]. Image-guided cryoablation of intercostal nerves has been shown in case-reports and series to decrease chronic pain following thoracotomy[31,32]. These findings suggest a role for percutaneous, imaging guided intercostal nerve cryoablation in patients with rib fractures who are poor candidates for SSRF and VATS-guided intercostal nerve cryoablation.

In 2019, Stanford received 3,132 trauma activations. Of these, 495 (16%) patients had rib fractures, and 267 (9%) had rib fractures and were ≥ 65 years. Over the last 6 months, we have used cryoablation of the intercostal nerve as an analgesic adjunct to SSRF among 6 patients with promising results. Given our experience with VATS-guided cryoablation of intercostal nerves, we hypothesize that CT-guided cryoablation of the intercostal nerve would provide a minimally invasive method of long-term pain control for these high-risk surgical patients, affording the benefits of cryoablation of the intercostal nerves, without the risk of surgery.

Study design:

We propose a randomized-controlled study comparing CT-guided percutaneous cryoablation of the intercostal nerves with standard-of-care to standard-of-care alone in elderly patients with acute rib fractures following chest wall trauma.

Enrollment:

Patients will be prospectively enrolled by the trauma service at the time of admission and followed through their hospital course. A random number generator will be used to select traumatically injured patients ≥ 65 years with rib fractures to either standard care or percutaneous cryoablation with standard care. Clinical data will be collected from patient's charts using a standardized reporting tool and quality-of-life data will be collected by telephone or during patient visits to the chest wall injury clinic.

Treatment group:

A consult would be placed to interventional radiology for evaluation for CT-guided cryoablation of the intercostal nerves. Patients who are deemed to be adequate candidates will be taken urgently for cryoablation (≤72 hours from enrollment). All subsequent care will be carried out by the trauma service according to standard of care.

Protocol Amendment September 2023

Intent to treat Enrollment Strategy:

Patients who meet all inclusion criteria, consent to participate in the trial, and are thus enrolled but who ultimately do not receive the procedure will be included in the treatment group and followed as all other participants in this group, per an intention-to-treat enrollment strategy. This change was requested on 9/22/23 due to issues of scheduling procedures on the weekends impacting enrollment and patients not tolerating lying prone.

Control group:

All patient care will be carried out by the trauma service according to standard-of-care. This includes admission to the ICU or ward at the discretion of the attending physician. Multimodal pain control including acetaminophen, gabapentin, and narcotic, and evaluation for neuraxial or regional nerve block by the anesthesia service as dictated by current clinical protocol.

Study Inclusion criteria include:

- patients ≥65 years with any acute rib fracture
- pain score ≥5 with deep inspiration

Study Exclusion criteria include:

- if only ribs broken are ribs 1,2 or 10,11, 12
- radiographic evidence of metastasis to ribs
- Glasgow Coma Scale (GCS) score <13
- patients undergoing SSRF
- rib fractures located <3 cm from spinous process
- coagulopathy (INR>1.5, Plt<100)
- other factors precluding cryoablation at IR attending's discretion

Treatment: Patient will go to interventional radiology for percutaneous cryoablation of ribs 3-9 on affected side. The Endocare™ 1.7mm Round Ice PerCryo™ Croprobe will be used. A post procedure chest x-ray will be obtained.

Power:
A recent study by Pieracci et al.[33] examined impact of SSRF vs. nonoperative management on outcomes among patients with ≥3 ipsilateral bicortical rib fractures. The authors found a reduction in numeric pain score (NPS) from 6.3 to 4.7 ($p<0.01$) and 4.5 to 2.9 ($p<0.01$) at one and two weeks, respectively, in patients who underwent SSRF. Assuming a standard deviation of 3 (assumption made by Pieracci et al.), 110 patients would be required to detect a 20% difference with alpha= 0.05. We estimate that the Stanford Trauma Service sees approximately 100 patients per year who would qualify for this study assuming a third of the persons aged ≥65 years with rib fractures would both qualify and consent to the study. There were 267 patients aged ≥65 years with rib fractures admitted in 2019.

Assessments:

Acute pain and pulmonary function:
Acute pain will be assessed by numerical pain score (NPS). Patients are asked to rate their pain on a scale of 0-10 with 0 being no pain and 10 being the worst pain. NPS is currently assessed as part of ongoing nursing evaluations and is recorded in the patient's chart. Pulmonary function will be assessed by incentive spirometry which is also charted in daily progress notes.

Chronic pain:
The McGill Pain Questionnaire (MPQ) is a validated 20 question instrument to quantify subjective pain. The scoring system yields a pain rating index (PRI) score between 0 and 50 used to temporally track pain[34]. This system has been in patients with chest wall injury[5,35] with PRI ≥8 being significant for chronic pain. MPQ PRI will be calculated upon study enrollment, at the time of hospital discharge, and at 30, 90, and 365 days following hospital discharge.

Long-term function:
The Glasgow Outcome Scale Extended (GOS-E)[36] is a widely used, standardized instrument developed to assess long-term outcomes in patients following traumatic brain injury (TBI). The scale provides a composite score (1-8, see **Figure 2**) based on multiple domains including social activities, ability to engage in relationships. Work status, ability to care for oneself and mobility within the community. The 12-Item Short-Form (SF-12) Health Survey[37] is another validated, widely used composite score to gauge overall health based on 8 domains. Both of these scales have been used in patients who have sustained chest wall trauma[5,35].

Patients will be assessed using the GOS-E in person at scheduled clinic visits or by telephone at 30, 90 and 365 days following hospital discharge.

Endpoints:

The primary endpoints of the study would be daily numeric pain score and length of hospital stay. Secondary endpoints for the study would include 30-day mortality, need for ICU, use of narcotic equivalents, 30 day rib-specific (delayed hemothorax, pneumothorax, pneumonia, pain) readmission, as well as long term pain and quality of life as measured by MPQ PRI, GOS-E and SF-12 scores at 30, 90, and 365 days.

Variables:

Variable	Dictionary*
Demographic	
MRN	Numerical
Age	Numerical; years
Sex	Categorical; M=0, F=1
Arrival time	MM/DD/YYYY/24HR time
Blunt vs Penetrating	Categorical; Blunt = 0, Penetrating = 1
Mechanism	Categorical; Fall = 0, MVC =1 , MCC=2, bicycle = 3, pedestrian vs auto = 4, blunt assault = 5, GSW= 6, Stab = 7, other = 8
Injury severity score	Numerical
Admission GCS score	Numerical
Intracranial hemorrhage	Categorical; N=0, Y=1
Facial fracture	Categorical; N=0, Y=1
Spine fracture	Categorical; N=0, Y=1
Pelvis fracture	Categorical; N=0, Y=1
Long bone fracture	Categorical; N=0, Y=1
Solid organ injury	Categorical; N=0, Y=1
BCVI	Categorical; N=0, Y=1
Randomization	
Median pain score in first 24 hours	Numerical
Lowest pain score in first 24 hours	Numerical
Highest pain score in first 24 hours	Numerical
Incentive spirometry	Numerical; cc
Cough	Categorical; 0 = none, 1 = weak, 2 = moderate, 3 = strong
Randomization group	Categorical; 0 = standard of care, 1 = intervention
Intervention time	MM/DD/YYYY/24HR time
Pain control pre-procedure	
Daily MME before intervention	Numerical
Thoracic epidural	Categorical; N=0, Y=1
Continuous intercostal nerve block	Categorical; N=0, Y=1
Paraspinal or paravertebral block or catheter	Categorical; N=0, Y=1
Ketamine gtt	Categorical; N=0, Y=1
Liposomal bupivacaine rib block	Categorical; N=0, Y=1
Lidocaine gtt	Categorical; N=0, Y=1
Lidocaine patch	Categorical; N=0, Y=1
Gabapentin	Categorical; N=0, Y=1
NSAIDs	Categorical; N=0, Y=1
Acetaminophen	Categorical; N=0, Y=1
Pre-existing illness	

COPD or asthma	Categorical; N=0, Y=1
BMI $\geq$ 30 kg/m^2	Categorical; N=0, Y=1
Current smoker	Categorical; N=0, Y=1
Diabetes	Categorical; N=0, Y=1
History of chronic chest wall pain	Categorical; N=0, Y=1
Prior rib fractures	Categorical; N=0, Y=1
Rib-specific injuries	
Side of rib fractures	Categorical; 0 = Left only, 1 = Right only, 2 = Bilateral
Open vs closed	Categorical; N=0, Y=1
Clinical flail chest	Categorical; N=0, Y=1
Radiographic flail	Categorical; N=0, Y=1
Number of rib fractures on L	Numerical
Location of fractures on L	Categorical; anterior = 0, lateral = 1, posterior = 2
Severity of rib fractures on L	Categorical; undisplaced = 0, offset = 1, displaced = 2
Number of rib fractures on R	Numerical
Location of rib fractures on R	Categorical; anterior = 0, lateral = 1, posterior = 2
Severity of rib fractures on R	Categorical; undisplaced = 0, offset = 1, displaced = 2
Pneumothorax	Categorical; N=0, Y=1
Chest tube in place	Categorical; N=0, Y=1
Hemothorax	Categorical; N=0, Y=1
Sternal fracture	Categorical; N=0, Y=1
Clavicle fracture	Categorical; N=0, Y=1
Scapula fracture	Categorical; N=0, Y=1
Hospitalization	
Hospital length of stay	Numerical; days
Admission to ICU	Categorical; N=0, Y=1
Length of ICU stay	Numerical; days
Need for intubation	Categorical; N=0, Y=1
Post procedure hemothorax	Categorical; N=0, Y=1
Post procedure pneumothorax	Categorical; N=0, Y=1
Post procedure pathology requiring chest tube	Categorical; N=0, Y=1
Surgical site infection	Categorical; N=0, Y=1
Post procedure pneumonia	Categorical; N=0, Y=1
Post procedure DVT	Categorical; N=0, Y=1
Discharge	
MME equivalents on day of discharge	Numerical
Gabapentin	Categorical; N=0, Y=1
Lidocaine patch	Categorical; N=0, Y=1
NSAIDs	Categorical; N=0, Y=1
Acetaminophen	Categorical; N=0, Y=1
Median pain score in last 24 hours	Numerical
Lowest pain score in last 24 hours	Numerical
Highest pain score in last 24 hours	Numerical
Incentive spirometry	Numerical; cc
Cough	Categorical; 0 = none, 1 = weak, 2 = moderate, 3 = strong
Discharge Day	MM/DD/YYYY/24HR time
Discharged to higher level of care than arrival?	Categorical; N=0, Y=1
Discharged to home	Categorical; N=0, Y=1
Discharged with home health	Categorical; N=0, Y=1
Discharged to SNF	Categorical; N=0, Y=1

Discharge to LTAC	Categorical; N=0, Y=1
Died in hospital	Categorical; N=0, Y=1
Follow up data	
Day of follow up	MM/DD/YYYY/24HR time
Daily MME usage	Numerical
Gabapentin use	Categorical; N=0, Y=1
Lidocaine patch	Categorical; N=0, Y=1
NSAIDs	Categorical; N=0, Y=1
Acetaminophen	Categorical; N=0, Y=1
McGill Pain Score	Numerical Sensory: X/33 Affective: X/12 Visual Analogue Scale: X/10 Present Pain Intensity: X/10
Glasgow Outcome Scale	Categorical; D = 0, VS = 1, SD- = 2, SD+ = 3, MD- = 4, MD+ = 5, GR- = 6, GR+ = 7
SF-12 PCS score	Numerical
SF-12 MCS score	Numerical
Incentive spirometry	Numerical; cc
Cough	Categorical; 0 = none, 1 = weak, 2 = moderate, 3 = strong
Winged scapula	Categorical; N=0, Y=1
Readmitted since last seen	Categorical; N=0, Y=1
Rib-specific admission?	Categorical; N=0, Y=1
Currently living at home	Categorical; N=0, Y=1
Currently living at home with assistance	Categorical; N=0, Y=1
Currently living at SNF	Categorical; N=0, Y=1
Currently living at LTAC	Categorical; N=0, Y=1
Died	Categorical; N=0, Y=1
Date of death	MM/DD/YYYY/24HR time

* will use a (.) for missing variables

Analysis Plan:

All statistical analysis will be performed with STATA. A single interim analysis will be performed at 50% enrollment. Analyses will be performed on both the intention-to-treat study population (which includes all enrolled participants, regardless of whether or not they received the treatment) as well as the per protocol analysis population (including only participants who actually received the treatment). Numerical variables will be expressed as mean (standard deviation) when normally distributed, and as median (interquartile range) when skewed. Categorical variables will be expressed as frequencies and percentages. Normal distribution will be assessed by the Kolmogorov-Smirnov test and visual inspection of histograms. Numerical values and categorical variables will be compared with the Mann-Whitney test and Fisher exact test respectively. Non-normally distributed data will undergo Box-Cox transformation. Any demographic or hospitalization variable with a P $\leq$0.1 on univariate analysis will be included in the multivariate model. A p-value of <0.5 is considered significant.

Database Protection: Participants are labelled with REDCap assigned participant IDs. Names, medical record numbers and ALL dates (dates of birth, admission, surgery and discharge) are removed from the REDCap database. Other HIPPA identifiers such as medication use and diagnostic results are present in the REDCap database for us to be able to evaluate the rib fracture in context of which treatment group the patient is assigned to. The REDCap database itself is a secure, password-protected database that is housed on Stanford servers. Furthermore only 3 members of the study team (Protocol Director and Data Administrator) have access to the code that can be used to indirectly link back to identifiers

Patient Safety:

The Protocol Director will be responsible for Data Safety and Monitoring for this study. The Protocol Director is a board-certified trauma and critical care surgeon with fellowship training in epidemiology. Adverse events including bleeding from injury to an intercostal artery, injury to an intercostal nerve, pneumothorax, neuroma, procedure site infection will be reviewed. Protocol deviations will be reviewed. At 50% enrollment, and interim analysis will be performed and reviewed for harm. The protocol director will report all Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), or Unanticipated Problems (UPs) to the IRB in accordance with FDA regulations. The Protocol Director will review any SAEs, SUSAR, or UP with the IRB. The Protocol Director will provide all interim data to the IRB for evaluation and approval. The study will end after 110 patients have been accrued, if the study is recommended to be stopped at interim analysis, or at the discretion of the IRB. The Protocol Director will disseminate outcomes of the review to the IRB and the protocol director.

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