Title: Intercostal Cryoneurolysis Following Traumatic Rib Fractures

NCT: NCT03917823

Date: February 19, 2020

UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: Feb. 19, 2020

1. PROJECT TITLE

Intercostal Cryoneurolysis following Traumatic Rib Fractures

2. PRINCIPAL INVESTIGATOR

Brian M. Ilfeld, MD, MS

3. FACILITIES

UCSD hospitals: Hillcrest, JMC, Thornton, and KOP

4. ESTIMATED DURATION OF THE STUDY

Three years (including follow-up and analysis)

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Rib fractures are one of the most common injuries in trauma patients. These fractures are associated with significant pain as well as decreased ability to inspire deeply or cough to clear secretions, which together lead to pulmonary complications and a high degree of morbidity and mortality. Peripheral nerve blocks as well as epidural blocks have been used with success to improve pain control in rib fracture patients and have been associated with decreased pulmonary complications and improved outcomes. However, a single-injection nerve block lasts less than 24 hours; and, even a continuous nerve block is generally limited to 3-4 days. The pain from rib fractures usually persists for multiple weeks or months. In contrast to local anesthetic-induced nerve blocks, a prolonged block lasting a few weeks/months may be provided by freezing the nerve using a process called "**cryoneurolysis**". The goal of this study is to evaluate the potential of cryoanalgesia to decrease pain and improve pulmonary mechanics in patients with rib fractures.

6. SPECIFIC AIMS

The ultimate objective of the proposed line of research is to determine if cryoanalgesia is an effective treatment for pain associated with rib fractures; and, if this analgesic modality improves pulmonary mechanics measured with incentive spirometry.

Specific Aim 1: **To determine if, compared with current and customary analgesia for rib fracture(s), intercostal nerve cryoneurolysis improves maximum inspiratory volume.**

Hypothesis 1a: The maximum inspired volume will be significantly *increased* on the day following the procedure [primary endpoint] as well as at other time points following the procedure [secondary end points] with intercostal cryoanalgesia as compared single-injection local anesthetic-based intercostal nerve blocks [measured with an incentive spirometer].

Hypothesis 1b: The maximum inspired volume as a percentage of the baseline will be significantly *increased* on the day following the procedure [secondary endpoint of greatest interest], as well as at other time points following the procedure [secondary end points] with intercostal cryoanalgesia as compared with single-injection local anesthetic-based intercostal nerve blocks [measured with an incentive spirometer].

Specific Aim 2: **To determine if, compared with current and customary analgesia, intercostal nerve cryoneurolysis decreases the pain associated with rib fracture(s).**

Hypothesis 2a: The *severity* of rib fracture pain *at rest* will be significantly decreased within the 12 months following the procedure with intercostal cryoneurolysis as compared with subjects receiving single-injection local anesthetic-based intercostal nerve blocks [measured using the Numeric Rating Scale for pain].

Hypothesis 2b: The *severity* of rib fracture pain *when using the spirometer or coughing* will be significantly decreased within the 12 months following the procedure with intercostal cryoneurolysis as compared with subjects receiving single-injection local anesthetic-based intercostal nerve blocks [measured using the Numeric Rating Scale for pain].

Hypothesis 2c: The *incidence* of chronic pain will be significantly decreased 6 and 12 months following a rib fracture with intercostal cryoeurolysis as compared with subjects receiving single-injection local anesthetic-based intercostal nerve blocks [measured using the Numeric Rating Scale for pain].

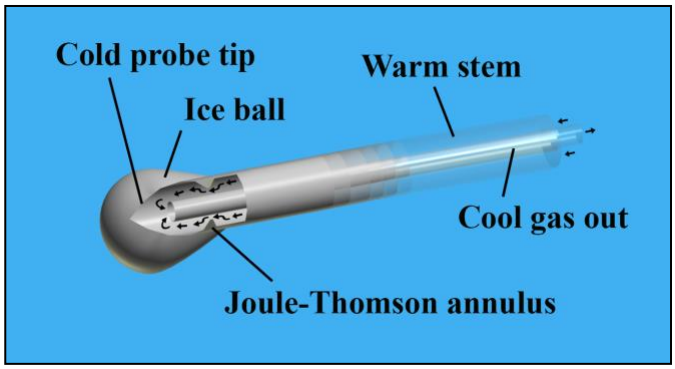
Hypothesis 2d: The *severity* of chronic pain will be significantly decreased 6 and 12 months following a rib fracture with intercostal cryoneurolysis as compared with subjects receiving single-injection local anesthetic-based intercostal nerve blocks [measured using the Numeric Rating Scale for pain].

7. BACKGROUND AND SIGNIFICANCE

Rib fractures represent a significant source of morbidity in trauma patients, with approximately 10% of trauma patients presenting with rib fractures.[1] Pain from rib fractures is associated with decreased ability to cough and inspire deeply, predisposing patients to atelectasis and pulmonary complications. Neuraxial blocks, both thoracic epidurals and paravertebral blocks, have been associated not only with decreased pain, but also decreased pulmonary complications and overall mortality in patients with rib fractures.[2] Furthermore, intercostal nerve blocks with local anesthetic have been shown to improve pain scores, peak expiratory flow rates, and arterial oxygen saturation on room air.[3] However, intercostal nerve blocks are not without risk and incidence of pneumothorax has been reported as 1.4% for each individual intercostal nerve that is blocked.[4] Although it is possible that the use of in-plane ultrasound guidance may decrease the risk of pneumothorax, this has not been evaluated. Additionally, intercostal blocks with bupivacaine have been reported to resolve in as little as six hours,[5] likely due to the high vascularity and consequent uptake of local anesthetic from the intercostal space.

An alternative analgesic technique is cryoneurolysis, consisting of the application of exceptionally low temperatures to *reversibly* ablate peripheral nerves, resulting in temporary pain relief termed “cryoanalgesia”.[6] The intense cold temperature at the probe tip produces Wallerian degeneration—a reversible breakdown of the nerve axon—subsequently inhibiting transmission of afferent and efferent signals. Because the nerve endoneurium, perineurium, and epineurium remain

intact, the axon regenerates along the exoskeleton at a rate of approximately 1-2 mm/day. While cryoneurolysis of peripheral nerves through surgical incisions has been commonly used to treat pain since 1961, the development of cryo probes that may be inserted percutaneously promise a revolution in the use of this modality. The combination of newly-designed narrow-gauge probes (upper right) and ultrasound now make percutaneous cryoanalgesia as simple as placing a peripheral nerve block: the probe tip is inserted adjacent to the target nerve under ultrasound guidance, and a series of 2-minute freezing cycles are administered followed by probe withdrawal. ***The procedure is essentially the same as placing an ultrasound-guided peripheral nerve block; however, instead of injecting local anesthetic, a gas circulates through the probe, inducing cold at the tip and freezing the target nerve.*** Nothing remains within the patient and there is no external equipment to prepare or manage. Importantly, cryoneurolysis and the probes are already approved by the United States Food and Drug Administration for the treatment of acute and chronic pain, so no additional regulatory approval is required for the proposed clinical trial.



Theoretical benefits of cryoneurolysis include an ultra-long duration of pain control without opioid involvement, no catheter management/removal (reducing infection risk), the lack of an infusion pump and anesthetic reservoir to carry, an extraordinarily-low risk of infection (approaching zero), and no risk of local anesthetic toxicity, catheter dislodgement or leakage. With a single 8-minute percutaneous cryoneurolysis procedure consisting of several freeze/defrost cycles, a truncation of sensory nerve conduction is induced for 6-8 weeks, with the complete restoration of nerve structure and function following remyelination. Cryoneurolysis offers the possibility of potent, side effect-free analgesia outlasting the surgical pain, and obviating the need for postoperative opioids.

8. PROGRESS REPORT

We have performed several cases in which cryoneurolysis was performed after rib fractures producing significant and long-lasting pain relief. All patients experienced significant pain relief immediately, continuing for at least 2 weeks post-intervention. Numeric Rating Scale pain scores were consistently improved from before the procedure for multiple weeks. No adverse events associated with cryoanalgesia were reported in any of the patients.

9. RESEARCH DESIGN AND METHODS

The cryoneurolysis procedure will be compared with our current UCSD standard practice.

Study Overview

Day 0	Baseline pain levels and spirometry Subjects randomized and cryoneurolysis/sham procedure administered Post-block pain levels and spirometry repeated

Days 1, 2, 7	Pain levels, opioid consumption, sleep disturbances due to pain, and incentive spirometry values collected [day of discharge recorded]
Months 0.5, 1, 1.5 , 2 3, 6, and 12	Pain levels, opioid consumption, sleep disturbances due to pain, and pain interference collected [if subject has spirometer available]

Subjects will be individuals who present to one of the UCSD hospitals with rib fracture(s) and significant pain. The University of Florida will be following the same protocol and the subjects from both institutions will be combined for the analysis. Those who consent to participate in this study will have standard ultrasound-guided intercostal nerve blocks administered with ropivacaine 0.5% (with epinephrine), 3 mL/level of each fracture rib as well as one level above and one level below.

Treatment group assignment (randomization). Subjects will be allocated to one of two possible treatments stratified by treatment center and unilateral vs. bilateral fractures:

1. ***active*** *cryoneurolysis (****sham*** *local anesthetic intercostal blocks)*
2. ***sham*** *cryoneurolysis (****active*** *local anesthetic intercostal blocks)*

Computer-generated randomization lists will be used to create sealed, opaque randomization envelopes with the treatment group assignment enclosed in each envelope labeled with the randomization number.

The specific intercostal nerves targeted will depend on the injury site. The treatment sites will be cleansed with chlorhexidine gluconate and isopropyl alcohol. Using the optimal ultrasound transducer for the specific anatomic location and subject anatomy (linear vs curvilinear array), the target nerves will be identified in a transverse cross-sectional (short axis) view. The intercostal nerve of each fractured rib as well as the level above and below will be treated with the protocol below:

Intercostal nerve block procedure: The target nerve will be visualized with ultrasound. Local anesthetic (1% lidocaine) will be used to infiltrate the skin and underlying muscle at each entry point. A 20 g Tuohy needle will be introduced through the skin wheel and along the anesthetized muscle tract. For subjects randomized to active cryo, 3 mL of normal saline will be injected into the muscle superficial to the nerve; and for subjects randomized to sham cryo, 3 mL of ropivacaine 0.5% (with epinephrine) will be injected perineurally to provide the intercostal nerve block.

Cryoneurolysis procedure: Cryoneurolysis probes are available for a console neurolysis device (PainBlocker, Epimed, Farmers Branch, Texas) that either (1) pass nitrous oxide to the tip inducing freezing temperatures; or, (2) vent the nitrous oxide at the base of the probe so that no gas reaches the probe tip, resulting in no temperature change. The latter is a sham procedure since without the temperature change, no ice ball forms and therefore the target nerve is not affected. An angiocatheter/introducer will be inserted beneath the ultrasound transducer and directed until the probe tip is immediately adjacent to the target nerve. The angiocatheter needle will be removed, leaving the angiocatheter through which the appropriate Epimed probe will be inserted until it is adjacent to the target nerve. The cryoneurolysis device will be triggered using 2 cycles of 2-minute gas activation (active or sham) separated by 1-minute defrost periods. For active probes, the nitrous oxide will be deployed to the tip where a drop in temperature to -70°C will result in cryoneurolysis. For the sham probes, the nitrous oxide will be vented prior to reaching the probe shaft, resulting in a lack of perineural temperature change.

The process will be repeated with the same treatment probe for any additional nerves (e.g., all nerves will receive either active cryoneurolysis or sham/placebo, and not a mix of the two possible treatments).

For subjects at the University of Florida, their anthropomorphic, baseline, procedure, and post-procedure data will be recorded on the same case report form as at the University California San Diego and faxed to the investigators at UC San Diego following the procedure. These faxed documents will remain in electronic form (eFax) on the Principal Investigator's password-protected, encrypted, UCSD-owned MacBook computer. Investigators at UC San Diego will do all of the follow-up data collection by phone for subjects at both treatment centers.

Outcome measurements (end points). Anesthesia providers will perform all measures and assessments, which will include:

1. **Pain:** measured on the 11-point NRS of pain intensity
2. **Opioid consumption**
3. **Pain interference:** measured using the Brief Pain Inventory (which includes the pain scores of #1 above)
4. **Sleep disturbances (#):** due to pain
5. **Pulmonary Mechanics:** measured by the inspired volume on a handheld incentive spirometer based on the American Association of Respiratory Care (AARC) clinical practice guideline.[7] The best of three measurements will be recorded as the maximum inspired volume.

Statistical Analysis: The primary endpoint is the maximum inspired volume measured by incentive spirometry the day following treatment. There is no accepted minimal clinically-relevant change in incentive spirometry volume. However, the median (IQR) of inspired volume for patients with rib fracture(s) is 1250 (750-1750) mL;[8] and, ISV<1000 mL is associated with an increased risk of acute respiratory failure.[8] We will therefore use the difference between 1250 and 1000 (250 mL) as the minimal clinically-relevant difference. However, there is high variability in the reported increase in inspired volume with various regional analgesic interventions such as continuous intercostal nerve blocks[9] and serratus plane blocks,[10] and we will therefore increase our enrollment to account for an unpredicted increase in variability or non-normal data distribution.

But, assuming a normal distribution, the interquartile range is approximately 1.35 standard deviations (SDs). Therefore an interquartile range of 250-50 = 200 mL (Hernandez et al. 2019) corresponds to, approximately, an SD of 200/1.35 = 148 mL. Assuming this SD of 148 mL, a sample size of n=7 per group provides 80% power to detect a group difference of d=250 mL per group with two sided Type 1 Error 5%. To allow for a larger-than-anticipated SD, we will enroll 10 subjects per group with an evaluable primary outcome measure (n=20 for both groups combined). Accounting for drop-outs, we request a maximum enrollment of 30 subjects.

"Continuous data will be summarized with mean, SDs, medians, quartiles, and ranges; and displayed with box-and-whisker plots by group and in aggregate. Key baseline characteristics will be

tested between groups using two-sample t-tests, and summarized with Cohen's D, for continuous measures; and Fisher's Exact test for categorical variables. The primary outcome is maximum incentive spirometry volume (ISV) measured in mL on POD 1. The group difference will be tested using Welch's two-sample test. Secondary outcomes will also be tested with the two-sample t-test. No multiplicity adjustments will be applied for these secondary outcomes. The Wilcoxon signed-rank test will be used as a sensitivity analysis. Secondary analyses will include a Mixed Model of Repeated Measures with fixed-effects for time, time-by-group, unilateral vs bilateral, and the number of fractures. The model will treat time as a categorical variable and will assume a compound symmetric correlation and heterogeneous variance with respect to time. The estimated mean difference between groups at the final scheduled timepoint will be the parameter of interest and will be tested using Kenward-Roger degrees of freedom. Out- comes only measured at baseline and a single follow-up timepoint will be analyses with Analysis of Covariance (ANCOVA). The dependent variable will be change from baseline, and covariates will include group, baseline outcome, unilateral vs bilateral, and the number of fractures. Missing data is not expected due to the short follow-up in this study. However, if missing data issues arise, we will use multiple imputation which is robust to covariate-dependent Missing at Random, and tipping point analyses under various Missing Not at Random assumptions."

10. HUMAN SUBJECTS

Inclusion criteria: Adult patients of at least 18 years of age, (1) having a total of 1-6 rib fractures at least 3 cm distal to the costo-transverse joint sustained within the previous 3 days (bilateral fractures are acceptable, but the total of the two sides combined must not exceed 6 fractures); (2) regional anesthetic requested by the admitting service; and, (3) accepting of a cryoneurolysis procedure.

Exclusion criteria: (1) chronic opioid use (daily use within the 2 weeks prior to surgery and duration of use > 4 weeks; of note, any testing for opioid use will not occur as part of the study, but as standard of care); (2) pregnancy; (3) incarceration; (4) inability to communicate with the investigators; (5) morbid obesity (body mass index > 40 kg/m^2); (6) possessing any contraindication specific to cryoneurolysis such as a localized infection at the treatment site, cryoglobulinemia, cold urticaria and Reynaud's Syndrome; (7) any patient unable to correctly perform incentive spirometry as this is the primary outcome measure; (8) any patient with any degree of decreased mental capacity as determined by the surgical service; (9) any reason an investigator believes study participation would not be in the best interest of the potential subject; (10) flail chest; (11) chest tube; (12) fracture of the 1^{st} rib on either side; or (13) any moderate or severe pain (NRS>3) unrelated to the rib fracture(s), as best determined by the patient and investigator.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Study inclusion will be proposed to eligible patients at one of the UCSD Medical Center hospitals (listed in #3 above)—by an investigator part of the clinical treatment team involved in the patient's clinical care (HIPAA requirements will be adhered to). There is no minimum number of hours or days from the time of fracture until the time of study participation and no requirement for overnight admission. If a patient desires study participation, written, informed consent will be obtained using an IRB-approved informed consent form.

Selection for inclusion will not be based on sex, race, or socioeconomic status. For women of childbearing age with the possibility of pregnancy, a sample of urine is always collected for a

pregnancy test prior to an invasive procedure—regardless of study participation. Pregnant patients will be excluded from study participation.

12. INFORMED CONSENT

When a prospective subject desires, they will be provided information on the study purpose and protocol, as well as have any questions answered. Candidates who meet inclusion and exclusion criteria and desire study enrollment will be scheduled for treatment, usually the same day or the following day depending on staff/equipment availability, anti-coagulation status, and other factors. Written informed consent will be attained prior to any measurements or procedures. This will occur in private patient care rooms, so that subjects may feel comfortable asking questions.

Subjects will be provided ample privacy and time for decision making. Surrogate consent will not be accepted; therefore, if human subjects cannot provide consent on their own, they will not be offered study enrollment. Consent by an individual's Legally Authorized Representative is unacceptable for study enrollment. Of note, minors (age < 18 years) will not be offered enrollment. Therefore, assent will not be accepted during the informed consent process.

13. ALTERNATIVES TO STUDY PARTICIPATION

Potential study subjects may simply decline enrollment. They will still receive our standard-of-care analgesics.

14. POTENTIAL RISKS

1. Infection. There is the potential risk of infection since subjects will have a probe inserted through the skin. Since there will be nothing left going through the skin or in the subject after the probe is withdrawn, the risk of infection is very small and there has never been a report of permanent injury due to infection following cryoneurolysis.
2. Bleeding. The probe does not have an open tip and is not particularly sharp, so there is a very low risk of having any type of bleeding as a result of treatment. However, if it was to happen, we would hold pressure until the bleeding stopped.
3. The skin where the nerve is frozen could lose or gain color if the nerve is particularly close to the surface. However, this has never been reported for deeper nerves and using the probe that will be used for this study.
4. Since a nerve will be frozen, there is the chance of nerve injury. However, in multiple decades of using percutaneous cryoneurolysis on peripheral nerves, only a single case of "neuritis" (nerve irritation) has been reported in medical journals, and this resolved after a few months.
5. There is the risk of loss of confidentiality. The following procedures will be done to maintain confidentiality: written, paper forms will be kept in a locked medical. Computerized records containing personal health information will be stored on password-protected and encrypted computers.
6. The intercostal nerves run on the under surface of the ribs. Inserting a cryoneurolysis probe close enough to freeze these nerves therefore has a risk of injuring the lining of the lung resulting in pneumothorax. The risk of pneumothorax during such a procedure with ultrasound guidance is estimated from the literature as 1 in 2,000. However, the anesthesiologists performing these procedures have advanced training and years of experience that should further reduce this risk.
7. Pain. Cryoneurolysis has been demonstrated to provide pain relief for various chronic pain indications; but, it has not been rigorously investigated for acute pain states such as rib fractures. Therefore, subjects randomized to receive cryoneurolysis of the intercostal nerve(s) might

experience more pain during the first 6-8 hours after treatment than subjects receiving a local anesthetic-based intercostal nerve block; but, they also might experience less pain for the remainder of 2 months during the period of fracture healing.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

During the treatment, subjects will be continuously monitored with pulse oximetry, noninvasive blood pressure cuffs, and EKG (standard for nerve blocks). If one is not already present, subjects will receive an IV so that emergency medications could be given, if needed. As described above, probes will be placed under sterile conditions as is standard-of-care for any percutaneous cryoneurolysis.

Following treatment, the subjects will be contacted daily for the first 2 days, and then on days 7 and 14,, as well as months 1, 1.5, 2, 3, 6 and 12. Subjects will have a physicians' pager and cellular phone numbers available to respond 24 hours/day and 7 days/week for at least the first week following treatment.

The risks to confidentiality are the release of names/ telephone numbers/ demographic data (e.g. weight, age, height), which will be minimized by the use of password-protected computers and case report forms that will be stored in locked offices.

Subjects will be given clear instructions to call an investigator with any questions or concerns regarding their study participation. If a patient experiences an injury that is directly caused by this study, medical care will be provided at the medical center. No other compensation is offered. Any adverse events will be reported to the IRB using the standard adverse events reporting and upon continuing review (depending on severity, as defined by the IRB).

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Disposition of data. The original, hard-copy signed informed consent forms and case report forms will be stored within an investigator's locked office; and they will remain with the Principal Investigator for at least 7 years. Data will be entered into an Excel spreadsheet kept on a password-protected and encrypted computer and retained by the Principal Investigator for at least 7 years.

17. POTENTIAL BENEFITS

For subjects randomized to receive a sham cryo treatment: There will be no difference between being in this study and deciding against participation. Therefore, there is no potential for direct benefits from this sham cryo "treatment".

For subjects randomized to receive active cryoneurolysis: It is our hope that patients have a decrease in their acute and chronic rib fracture pain (which might permit a decreased opioid consumption and opioid-related nausea/vomiting) and improved pulmonary mechanics measured by incentive spirometry.

Possible benefits to others: Future patients may benefit if it is determined that cryoneurolysis decreases pain and improves pulmonary function in patients with rib fractures. In addition, with the opioid epidemic, any decrease in opioid requirements would be a welcome development.

18. RISK/BENEFIT RATIO

Pain associated with rib fractures is often severe and debilitating. This pain makes it difficult for these patients to breathe deeply and cough to clear pulmonary secretions, which contributes to a high degree of morbidity and mortality in these patients. Since cryoneurolysis has a very low incidence of complications, and there have no previous cases of permanent negative sequelae reported in the literature, we believe the potential risks to be minimal compared to the potential benefits. There is the risk of less analgesia for the first 6-8 hours for subjects receiving active cryoneurolysis vs. those receiving active local anesthetic-based intercostal nerve blocks, but since cryoneurolysis results in a sensory block of the nerve due to Wallerian degeneration, we deem this risk to be extremely small.

Subjects will be given clear verbal and written instructions to call Dr. Ilfeld or Dr. Finneran in the Department of Anesthesia at UCSD, with any questions or concerns regarding their study participation. If a patient experiences an injury that is directly caused by this study, they will receive professional medical care at the University of California, San Diego. No other compensation is offered. Any adverse events will be reported to the UCSD IRB using the standard adverse events reporting website and on continuing review (depending on severity, as defined by the IRB).

19. EXPENSE TO PARTICIPANT

There will be no additional costs to subjects as a result of being in this study.

20. COMPENSATION FOR PARTICIPATION

There is no compensation for participation.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Principal Investigator, **Brian M. Ilfeld, MD, MS,** is a board-certified anesthesiologist with fellowship training in and 18 post-training years of experience with regional anesthesia and acute pain medicine. Dr. Ilfeld holds a license to practice medicine in California. Dr. Ilfeld has medical privileges at the UC Medical Centers. Dr. Ilfeld, or another investigator, will follow all subjects following their treatment. Dr. Ilfeld will be responsible for the overall management of this study, as well as for the well-being of study subjects.

Co-investigators, **John Finneran MD, Rodney Gabriel MD, MS, and Matthew Swisher, MD,** are board-certified or -eligible anesthesiologists with experience with regional anesthesia and acute pain medicine. All hold a license to practice medicine in California and medical privileges at the UC Medical Centers. All will help consent subjects, perform a history and physical exam, perform the treatment on subjects, and will follow subjects following their treatment.

Jay Doucet, MD, Sara Edwards, MD, Todd Costantini, MD, and Allison Berndtson, MD are board-certified surgeons and hold licenses to practice medicine in California and medical privileges at the UC Medical Centers, and will help enroll subjects, perform the history and physical exam, and follow-up with subjects.

Baharin Abdullah and **Jeffrey Mills** are research coordinators with the UCSD CTRI, with the required training—including up-to-date CITI training—for their positions.

22. BIBLIOGRAPHY

1. Ziegler DW, Agarwal NN. The morbidity and mortality of rib fractures. J Trauma. 1994; 37: 975–979.

2. 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; 124(6): 1906-1911.

3. Osinowo OA, Zahrani M, Softah A. Effect of intercostal nerve block with 0.5% bupivacaine on peak expiratory flow rate and arterial oxygen saturation in rib fractures. J Trauma Acute Care 2004; 56(2): 345-347.

4. Shanti C, Carlin A, Tyburski J. Incidence of Pneumothorax from intercostal nerve block for analgesia in rib fractures. J Trauma Acute Care 2001; 51(3): 536-539.

5. Pedersen VM, Schulze S, Høier-Madsen K, Halkier E. Air-flow meter assessment of the effect of intercostal nerve block on respiratory function in rib fractures. Acta Chir Scand 1983; 149:119-120.

6. Gabriel RA, Finneran JJ, Asokan D, Trescot AM, Sandhu NS, Ilfeld BM. Ultrasound-guided percutaneous cryoneurolysis for acute pain management: a case report. A A Case Per. 2017; 9: 129-132.

7. Restrepo RD, Wettstein R, Wittnebel L, Tracy M. Incentive spirometry: 2011 (AARC Clinical Practice Guideline). Respir Care 2011; 56: 1600-1604.

8. Butts CA, Brady JJ, Wilhelm S, Castor L, Sherwood A, McCall A, Patch J, Jones P, Cortes V, Ong AW. Do simple bedside lung function tests predict morbidity after rib fractures? Am J Surg 2017; 213: 473-477.

9. Lynch N, Salottolo K, Foster K, Orlando A, Koola C, Portillo V, Tanner A, Mains CW, Bar-Or D. Comparative effectiveness analysis of two regional analgesia techniques for the pain management of isolated multiple rib fractures. J Pain Research 2019; 12: 1701-1708.

10. Hernandez N, de Haan J, Clendeninn D, Meyer DE, Ghebremichael S, Artime C, Williams G, Eltzschig H, Sen S. Impact of serratus plane block on pain scores and incentive spirometry volumes after chest trauma. Local Reg Anest 2019; 12: 59-66.

23. FUNDING SUPPORT FOR THIS STUDY

None.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not applicable since percutaneous cryoneurolysis and the products used for this protocol are all cleared by the United States Food and Drug Administration for use treating both acute and chronic pain. Therefore, this is an on-label study.

26. IMPACT ON STAFF

Participants will be enrolled by investigators and no other staff are required for this study. Therefore there will not be an impact on hospital staff.

27. CONFLICT OF INTEREST

None.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable.

29. OTHER APPROVALS/REGULATED MATERIALS

None.

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Not applicable: surrogate consent will not be accepted.