COMIRB Protocol

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
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Protocol #: 17-1432
Project Title: A Multicenter, randomized controlled trial of surgical stabilization of rib fractures in patients with severe, non-flail fracture patterns (CWIS NON-FLAIL)
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I. Hypotheses and Specific Aims: The objective of this trial is to investigate the efficacy of surgical stabilization of rib fractures (SSRF), as compared to non-operative management, for hospitalized patients with non-flail, severe rib fractures. The study will be conducted within expert, high volume centers that participate in the Chest Wall Injury Society (CWIS). The hypothesis of this trial is that SSRF, as compared to standardized non-operative management, improves pulmonary function, risk of complications, quality of life, pain control, and reduces the need for opioid pain medication among patients with severe, non-flail chest fracture patterns.

II. Background and Significance: Rib fractures are the most common serious injury following blunt trauma, and occur in approximately 10% of trauma patients [1]. Despite improvements in the care of rib fracture patients, outcomes remain poor and have not changed substantially over the last 15 years [2]. Poor outcomes resulting from rib fractures include both acute complications (e.g., pneumonia, prolonged mechanical ventilation, and death) and chronic disability (e.g., pain, dyspnea, and loss of productivity).

Over the last 10 years, surgical stabilization of rib fractures (SSRF) has emerged as a promising technology for the management of patients with severe chest wall injuries [3]. Conceptually, SSRF applies the fundamental orthopedic principles of reduction and fixation to rib fractures, restoring chest wall stability and minimizing pain with respiration, splinting, and secretion accumulation. The advent of muscle-sparing [4] and even minimally-invasive surgical techniques [5], as well as a relatively low complication rate [6], has improved the appeal of this operation.
To date, three randomized clinical trials (RCTs) [7-9] and three meta-analyses of these and other trials [10-12] have limited their scope to patients with flail chest, a specific clinical diagnosis characterized by paradoxical motion of a portion of the chest wall due to fractures of two or more ribs in at least two places. Flail chest represents the most severe form of chest wall injury, with an associated, very high morbidity and mortality. Each of the aforementioned RCTs, as well as multiple prospective, non-randomized investigations [13, 14], have found a benefit to SSRF as compared to best medical management in this patient population. Accordingly, expert consensus statements have recommended this operation in this subset of patients [3, 15].

Based upon the favorable reported efficacy of SSRF in patients with flail chest, many surgeons have broadened indications to patients with severe, non-flail rib fracture patterns, most commonly ≥ 3 severely displaced fractures. Although these injuries differ anatomically from flail chest, many of the same pathophysiologic principles are at work: namely, painful motion at the fracture sites that cause respiratory compromise, bony bridging [16], and risk of subsequent non-union, chronic pain, and restrictive lung disease. However, it is not clear if stabilization of these fractures confers the same benefits as in the case of flail chest. This lack of efficacy data has been recognized in recent guidelines, which were unable to recommend SSRF for non-flail fracture patterns pending further data [15]. Furthermore, long term quality of life data for both flail and non-flail fracture patterns managed with SSRF are not available.

The use of SSRF is increasing exponentially. Somewhat alarmingly, nearly one half of the procedures were performed in patients without flail chest [17]. A combination of the favorable results observed for SSRF in flail chest, the increasing prevalence of SSRF for non-flail chest, and the lack of quality evidence to support this operation in this patient population, lead to the design of the current RCT.

**III. Preliminary Studies/Progress Report:** Our group has previously conducted a similar, single institution, observational study, which included mostly patients with flail chest, but also approximately 20% of patients without flail chest [13]. In this study, SSRF was beneficial. Other groups have reported favorable outcomes with SSRF in non-flail chest patients, although these patients have comprised a small minority of the total patients in the study group [14].
IV. Research Methods

A. Outcome Measure(s):

**Primary Outcome: Chest Wall Specific Quality of Life Questionnaire:** Obtained at two week, one month, and two month follow up visits (*Attachment 1*).

**Secondary Outcomes:**

1. **Numeric pain score:** Obtained daily while hospitalized, and at two week, one month, and two month follow-up

2. **Narcotic use:** Obtained daily while hospitalized, and at two week, one month, and two month follow-up visits and using a standardized equi-analgesic scale (*Attachment 2*)[18].

3. **Incentive spirometry:** Obtained daily while hospitalized, and at two week, one month, and two month follow-up visits (*Attachment 3*). The best value of three attempts will be used.

4. **Pulmonary function testing:** Obtained once at 2 week follow-up visit

5. **SF-36 Quality of Life Questionnaire, adjusted for rib injury:** Obtained at two week, one month, and two month follow-up visit (*Attachment 4*).

B. Description of Population to be Enrolled:

**Inclusion Criteria:**

In an effort to identify non-flail rib fracture patients for whom there is relative equipoise for SSRF vs. non-operative management, the CWIS conducted a survey of surgeons who perform SSRF regularly [19]. The survey presented a series of hypothetical trauma patients with non-flail chest, severe rib fractures. Patient age, degree of traumatic brain injury, and number of deranged pulmonary physiologic variables at the time of consideration for surgery were varied, and respondents were asked if they would recommend SSRF. The degree of consensus which most closely approximately true equipoise was 44.8%; this hypothetical scenario involved a patient with
≥ 3 fractures with at least 50% displacement, aged 18 – 90 years, and with either no or mild traumatic brain injury (TBI). This hypothetical patient served as the basis for our inclusion criteria:

1. Hospitalization with ≥ 3 severely displaced (≥ 50% of rib width) acute rib fractures.

2. Two or more of the following pulmonary physiologic derangements (at the time of consideration for enrollment and after best medical therapy).
   a. Respiratory rate > 20 breaths per minute
   b. Incentive spirometry < 50% predicted (Attachment 3)
   c. Numeric pain score > 5
   d. Poor cough (as documented by respiratory therapist)

3. Surgery anticipated < 72 hours from injury

**Exclusion Criteria:**

1. Age < 18 years or ≥ 80 years

2. Flail chest: either radiographic or clinical. Radiographic flail chest is defined on CT chest as ≥ 2 ribs each fractured in ≥ 2 places. Clinical flail is defined as visualization of a segment of chest wall with paradoxical motion on physical exam.

3. Moderate or severe traumatic brain injury (Intra-cranial hemorrhage visualized on CT head with GCS at the time of consideration for enrollment < 12)

4. Intubation

5. Severe pulmonary contusion, defined as Blunt Pulmonary Contusion 18 (BPC18) score > 12 [20].

6. Prior or expected emergency exploratory laparotomy during this admission.

7. Prior or expected emergency thoracotomy during this admission.
8. Prior or expected emergency craniotomy during this admission.

9. Spinal cord injury

10. Pelvic fracture that has required, or is expected to require, operative intervention during this admission.

11. The patient was unable to accomplish activities of daily living independently prior to injury (e.g., dressing, bathing, preparing meals).


13. Incarceration.

C. Study Design and Research Methods

Study type: Multicenter, randomized, non-blinded, clinical trial, with reserved option to collect data prospectively on subjects who decline randomization.

Study Arms:
1. Standardized best medical management of rib fractures

2. Standardized best medical management of rib fractures plus surgery (SSRF)

Participating Centers: Recently, the CWIS was formed as an international group of expert chest wall surgeons (www.cwisociety.org). The CWIS membership is comprised of experienced, high volume SSRF surgeons with established successful protocols, pathways, and outcomes of patients with severe rib fractures. This group is also academic, published, and driven to conduct high quality research to refine the indications for SSRF. Participating centers were identified through the CWIS research committee based upon these criteria.

Standardization of management protocols

Both groups (SSRF and medical management) will receive identical non-operative management, including standardized analgesic and pulmonary toilet protocols.
Standardized analgesia will include 1) standing acetaminophen 650 mg PO Q6h; 2) standing ibuprofen 600 mg PO q6H; 3) standing gabapentin 300 mg PO tid 4) one of the following locoregional modalities a) thoracic epidural catheter; 2) pain catheter (i.e., on-Q pump); c) liposomal bupivacaine rib blocks. Beyond these medications, narcotics will be administered as needed and abstracted as an outcome variable. Additional modalities (e.g., IV ketamine) will be discouraged but abstracted when used. Standardized pulmonary toilet will include hourly incentive spirometry and cough assist q4 hours.

For the SSRF group, the surgery will be standardized as follows: 1) flexible bronchoscopy on all patients; 2) muscle sparing incision whenever possible; 3) repair of all displaced fractures of ribs 3-8; 4) pleural irrigation with 500 mL sterile saline; 5) pleural drainage with either straight chest tube or siilastic drain (18F – 24F); 6) loco-regional anesthesia using one of the above modalities.

**Randomization:** Randomization will be accomplished at the lead study center (Denver, CO) using a standard function in Microsoft Excel that randomly chooses either the number 0 or 1. Each center will receive their own randomization log, such that approximately 50% of subjects from each center are randomized to surgery.

Of note, we anticipate a relatively high rate of declining randomization (approximately 50%). As such, we have incorporated a secondary, observational option for patients who decline randomization. In this arm, the decision to perform SSRF will be clinical, and left to the patient and their treatment team. Whatever that decision is, patients will be asked if they agree to prospective data collection, including the same endpoints as those randomized.

**Sample size calculation, trial feasibility, and projection duration:**

Sample size calculations for the primary and secondary outcome variables are shown below. The largest N total of 74 was selected and rounded up to 100 to maximize the likelihood of obtaining a significant difference. The mean annual number of SSRF performed per study center on patients who meet study criteria is 18. Assuming a 40% study decline rate, this would involve each center
enrolling 11 patients over a one year time. The study is thus feasible and powered to achieve target sample size in one year.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Mean (SD) non-op</th>
<th>Mean (SD) op</th>
<th>Alpha</th>
<th>Beta</th>
<th>N / group</th>
<th>N total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numeric pain score</td>
<td>3 (3)</td>
<td>5 (3)</td>
<td>0.05</td>
<td>0.80</td>
<td>37</td>
<td>74</td>
</tr>
<tr>
<td>Incentive spirometry</td>
<td>650 (300)</td>
<td>850 (300)</td>
<td>0.05</td>
<td>0.80</td>
<td>24</td>
<td>48</td>
</tr>
<tr>
<td>(mL)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>FEV1 % pred (PFTs)</td>
<td>67% (20%)</td>
<td>85% (20%)</td>
<td>0.05</td>
<td>0.80</td>
<td>16</td>
<td>42</td>
</tr>
<tr>
<td>Overall QOL</td>
<td>6 (2)</td>
<td>8 (2)</td>
<td>0.05</td>
<td>0.80</td>
<td>17</td>
<td>34</td>
</tr>
</tbody>
</table>

**Study Conduct:**

The study will be conducted and reported in accordance with the recommendations of the Consolidated Standards of Reporting Trials Statement [21] and registered with the U.S. National Institutes of Health (clinicaltrials.gov). The study will be approved by the Colorado Multiple Institution Review Board (COMIRB) and each sub site’s IRB. An independent data safety monitoring committee, comprised of four members of the CWIS (but not involved in the trial) will submit written reports to COMIRB and the study sponsor every six months. Adverse events will be recorded and reported to both the data safety monitor and COMIRB. No interim analysis is planned.

Each satellite site will contact the lead site PI or RC to obtain approval to proceed with consenting each subject, based on a review of the patient’s injury mechanism, fracture pattern, and inclusion/exclusion criteria.

**D. Description, Risks and Justification of Procedures and Data Collection Tools:**

**Surgical stabilization of rib fractures:** This is an approximately two hour operation that occurs under general anesthesia. Fractures of ribs 3-10 are repaired using thin, titanium plates through
small incisions that minimize muscle division. These plates are permanent. During the surgery, any blood that has accumulated in the pleural space will also be irrigated and suctioned out. Loco-regional pain control will also be administered as either rib blocks or an indwelling pain catheter. Finally, bronchoscopy will be performed to suction out any mucous which may have accumulated in the lungs as a result of not taking deep breaths. Risks of surgery include post-operative pain, bleeding, infection, and movement of the plates. Bleeding, infection, and movement of the plates are each very rare, and occur in less than 1% of patients who undergo the procedure. The surgeons at Denver Health have performed approximately 120 operations to treat rib fractures with plates.

**Pulmonary function tests**: The subject will be asked to breath into a straw-like tube and values are recorded. This is non-invasive and painless. Some shortness of breath after the test is completed may occur and resolves after a few seconds. The testing is administered by certified respiratory therapists at Denver Health.

**Justification of procedures**: SSRF is an established surgery for the treatment of severe rib fractures, and is recognized as such in expert consensus statements [3]. There exists equipoise regarding the benefit of SSRF in the specific study population targeted for this trial [19]

**E. Potential Scientific Problems:**

The main anticipated problem is a relatively high rate of declining randomization to operative vs. non-operative arms. We anticipate that approximately 50% of eligible patients approached will decline randomization. In anticipation of this, we have added an observation arm to the study; patients who decline randomization will be asked permission to collect their data throughout the same two month follow up period. In this case, treatment assignment to operative vs. non-operative is at the discretion of the patient and their treatment team.

Additional problems include coordination of a multiple site study- the investigators have budgeted into the grant a 1.0 FTE research coordinator whose sole responsibility will be this study.
Finally, standardization of management protocols, specifically both operative and non-operative. Standardized protocols will be distributed and monitored for adherence. Furthermore, a site initiation questionnaire has been drafted and will be completed by all centers interested in participation. Centers will be selected based on homogeneity in responses.

**F. Data Analysis Plan:** A standardized data collection tool will be used (Firefly Labs LLC). A sample data collection tool is attached (Attachment 5). All statistical analysis will be conducted using SAS version 9.4 (SAS Inc., Carey, NC). Statistical significance will be defined as $p < 0.05$. The distribution of continuous variables will be accessed for normality using the Kolmogorov-Smirnov test. Normally distributed continuous variables will be compared using the student's $t$-test. Non-normally distributed variables will be compared using the Wilcoxon Rank test. Categorical variables will be compared using the chi-squared test, unless expected cell counts were $< 10$, in which case Fischer's exact test was used.

Patients from both the randomized and observational cohorts will be grouped together in one analysis, and separately in a sub group analysis. The randomized and observed groups will be compared with respect to demographics, injury patterns, and rib fracture severity to unmask any potential biases.

**G. Summarize Knowledge to be Gained:** SSRF is being performed increasingly outside of the indication of flail chest. Although there may be benefit to SSRF in patients without flail chest, there exists equipoise in this specific patient population as recognized by surveyed members of CWIS. We believe that it is imperative to establish evidence to support this operation in this patient population.
H. References:


