Study Protocol

Steroid Administration for Articular Fractures of the Elbow (SAFE Trial): A Randomized, Controlled Trial of Perioperative Glucocorticoids during Treatment of Intraarticular Elbow Fractures

Principal Investigator:	Jed I. Maslow, MD
	Assistant Professor, Orthopaedic Surgery

Protocol Identification Number:	210125
Clinicaltrials.gov Identifier:	NCT04738318
Version Date	12/06/2022

Steroid Administration for Articular Fractures of the Elbow (SAFE Trial): A Randomized, Controlled Trial of Perioperative Glucocorticoids during Treatment of Intraarticular Elbow Fractures

Principal Investigator:
Jed I. Maslow, MD
Assistant Professor of Orthopaedic Surgery
Vanderbilt Department of Orthopaedic Surgery
MCE, S. Tower, Ste. 3200
Nashville, TN 37232-8828

Research Locations:

Vanderbilt University Medical Center 1211 Medical Center Drive, Nashville, TN 37232 Vanderbilt Health Belle Meade 6002 Highway 100, Nashville, TN 37205 Vanderbilt Orthopaedics Franklin 206 Bedford Way, Franklin, TN 37064 Vanderbilt Surgery Center Franklin 225 Bedford Way, Franklin, TN 37064	Vanderbilt Orthopaedics Lebanon Clinic 1616 West Main St, Suite. 300 Lebanon, TN 37087 Vanderbilt Wilson County Surgery Center 1401 West Baddour Pkwy Lebanon, TN 37087 Vanderbilt Wilson County Hospital - Operating Suite 1411 West Baddour Pkwy, Suite 1427 Lebanon, TN 37087 Vanderbilt Orthopaedics Hendersonville 128 North Anderson Lane Hendersonville, TN 37075

Table of Contents:

1.0 Background

Elbow fractures are complex injuries that often involve the articular surface, are in close proximity to critical neurovascular structures, and are prone to post-operative complications. Complications following treatment of intra-articular elbow pathology can affect over 50% of patients and up to 30% of all patients will require a re-operation. One of the most common complications is joint stiffness.[1] When a flexion arc of motion is diminished to less than 100 degrees, a flexion contracture is present greater than 30 degrees, or forearm rotation is less than 100 degrees, functional limitations are frequently present and further treatment may be recommended.[2,3] In fact, contracture release may be required in 12-20% of patients after intra-articular elbow fractures and carries a relatively high complication rate when performed.

The relationship of post-traumatic elbow contracture to intra-articular fractures is well established and can caused by extrinsic factors such as heterotopic ossification (HO), fibrosis and capsular thickening, or by intrinsic factors such as failure of nonunion, malunion, arthrosis, or loose bodies.[2,4] Recent studies analyzing the acute phase synovial fluid cytokine profile after an intra-articular elbow fracture have shown proinflammatory and catabolic factors in high concentrations that can lead to contracture through myofibroblast differentiation and proliferation.[4] Furthermore, HO can limit range of motion in up to 40% of fractures and may also result from prolonged inflammation with elevated IL-1β and TNF-α levels.

2.0 Hypothesis and Specific Aims

Primary Study Questions

a. For adult patients (>18yo) who sustain intra-articular elbow fractures (radial head, proximal ulna, distal humerus, or combined) that undergo operative fixation, does perioperative glucocorticoid administration (IV intra-operative followed by a post-operative oral taper course) improve post-operative range of motion (flexion/extension and pronation/supination) compared to a placebo?

Secondary Study Questions

b. Is perioperative glucocorticoid administration more effective in improving range of motion for certain intra-operative elbow fractures or depending on the mechanism of injury (subgroup comparison based on fracture type and high-energy or low-energy injuries)?

c. Do patients that receive perioperative glucocorticoids have a higher surgical site infection rate?

Hypothesis

1. Alternative: In adult patients with intra-articular elbow fractures, peri-operative dexamethasone administration will improve post-operative active range of motion early (≤6 weeks) and at final follow-up (≥6 months).
2. Null: In adult patients with intra-articular elbow fractures, peri-operative dexamethasone administration will not improve post-operative active range of motion early or at 6 month follow-up.

3.0 Animal Studies and Previous Human Studies

Prior investigators have sought to improve post-operative range of motion by modulating the inflammatory cascade. Desai et al. performed a retrospective review of 26 patients with a terrible triad injury (radial head fracture, coronoid fracture, and elbow dislocation) treated either with or without perioperative dexamethasone. The authors noted a significant improvement in the elbow arc of flexion (132.5° vs 105.5°) and in pronosupination (165.8° vs 132.2°) with no difference in infection rate.[5] Other animal studies have shown improved range of motion and decreased fibrotic reactions after joint immobilization in subjects treated with dexamethasone compared to controls.[6] Studies involving hip and knee arthroplasty have also shown a dose effect of dexamethasone in improving range of motion and reducing inflammatory cytokines.[7,8] Currently, no prospective studies of intra-operative or post-operative glucocorticoid use in upper extremity intra-articular fractures exist.

4.0 Inclusion/Exclusion Criteria

Inclusion Criteria

- All adults ≥18 years old with an intra-articular traumatic elbow fracture to be treated with operative intervention and a standardized post-operative rehab protocol
    - Intra-articular elbow fracture defined as:
        - Distal humerus
        - Proximal ulna
        - Radial head fracture
        - Combination fracture of two or more of the above
    - Radiographs present confirming intra-articular injury

Exclusion Criteria

- Patients with bilateral elbow fractures
- Patients with an altered mental status
- Pregnant
- Allergy or contra-indication to glucocorticoid administration
- Type 1 or Type 2 diabetes
- Pre-injury limitation in elbow range or motion (patient reported)
- Unable to provide consent for themselves

5.0 Enrollment/Randomization

General inclusion/exclusion criteria will be used to determine patient eligibility for this study. Potential study participants will be identified when they present to Vanderbilt University Medical Center or Vanderbilt Orthopaedic outpatient clinics for operative treatment of their intra-articular traumatic elbow fracture.

In-person Consent Process:
When a patient is determined to be eligible for the study, study personnel will approach the patient about taking part in the study. If the patient agrees to participate in the study, they will be provided with an informed consent document to review. The consent process will be conducted using either 1) a paper version of the appropriate consent form or 2) a REDCap-based electronic consent form. The electronic consent form has been developed in REDCap, a secure, web-based, HIPAA-compliant, data collection platform with a user management system. The REDCap-based electronic consent form can be accessed by research personnel using any electronic device. Eligible patients will be given an opportunity to ask questions about the study. If the patient agrees to participate in the study by signing the informed consent document, they will be provided with a copy of the signed consent form for their records.

Electronic Consent Process:
In the event a potential study candidate is missed during a consultation ER or outpatient clinic visit, or research personnel are unavailable to consent in-person, study personnel will contact the subject by phone to notify them of their study eligibility and ask if they would be interested in taking part. If the subject is interested in taking part in the study, study personnel will send a link to the REDCap-based electronic consent form by e-mail. If the subject agrees to take part in the study after reading the informed consent document, there will be an option for them to electronically sign their name and date the informed consent document. Once they electronically sign the electronic informed consent document, they will be given an option to save or print the signed electronic informed consent documents for their files.

Mail Consent Process:
If the subject does not wish to provide their email address, they will be sent two copies of the informed consent document by mail. If they agree to take part in the study, they will be asked to sign one copy and return it by fax or mail, and they will retain the second copy for their files.

Screening Form
Once the patient has signed the informed consent document, the study team will document subject eligibility by completing the REDCap Screening Form. This step will ensure only eligible patients are included in the study. The REDCap screening form will be completed prior to randomization activities.

Enrollment Goal
We will seek to enroll 18 patients in each treatment arm per fracture type and 18 patients in each control arm, for a total of 144 patients.

Fracture Type	Treatment Arm	Control Arm	Total
Distal humerus fracture	18	18	36
Radial head	18	18	36
Proximal ulna	18	18	36
Combined	18	18	36
			144

Randomization
Patients will be randomized according to a stratified permuted block randomization with a block size of 4. Randomization will be stratified based on fracture type: radial head, distal humerus, proximal ulna, combined. Treatment A will receive glucocorticoid and Treatment B will receive placebo. There will be 9 total blocks per fracture type, for 36 patients in each fracture-type strata and an even balance in all 4 strata, for 18 in each treatment arm.

Randomization will take place after consent. A randomization allocation table will be uploaded into REDCap. Randomization will be conducted by an Orthopaedic research coordinator. The treating physician, study research coordinator and patient will be blinded to the treatment assignment.

6.0 Study Procedures

Enrollment Visit
In addition to the enrollment and randomization procedures noted in Study Protocol Item 5.0, patient demographics and injury information will be documented as part of the patient's baseline assessment. Patient demographics will be imported from eStar into the REDCap database using the REDCap Clinical Data Interoperability Services (CDIS) tools.

Operative Visit
Preoperative-
Patients will be counseled regarding the possible adverse effects of the methylprednisolone and will be instructed to stop taking the drug immediately if they begin to experience the following adverse effects: skin rash, vision problems, muscle weakness, swollen face. The total dose up to stoppage will be recorded.

Intraoperative-
Patients will receive either a single intraoperative dose of 10mg of intravenous dexamethasone (Treatment A) or a single intraoperative dose of 10 mg of saline (Treatment B) based on their randomization allocation.

Postoperative
Discharge or Hospitalization
Following surgery, the participant will be provided with either a 1) six-day oral methylprednisolone taper course (Treatment A) or a six-day placebo course (Treatment B). Both medications will be in identical packaging. If the patient is admitted to the hospital following surgery, they will take the taper or placebo course as a home medication.

Day 0 (Day of surgery): 24mg oral dose, once daily
Day 1: 20mg oral dose, once daily
Day 2: 16mg oral dose, once daily
Day 3: 12mg oral dose, once daily
Day 4: 8mg oral dose, once daily
Day 5: 4mg oral dose, once daily

Day 6- Patients will be contacted by phone to assess compliance and experience (adverse effects).

Follow-up Clinic Visits
Based on routine care, patients will follow-up in the outpatient clinic at the following post-operative intervals: 2-week, 6-week, 3-month, and 6-month follow-up. The following data points will be collected at the routine care appointments:

- Active range of motion measurements by treating surgeon using a universal goniometer
    - Flexion/extension arc (degrees)
    - Pronation/supination arc (degrees)
- Surgical site infection requiring treatment (antibiotics or debridement: Y/N)
- Revision surgery (Y/N)
- Numeric pain score (0-10)
- Patient reported outcome Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) score
- Radiographic evidence of heterotopic ossification (present Y/N)
- Other complication not requiring revision surgery (nonunion, malunion, hardware failure, neuritis, synostosis)

If a participant misses a routine care postoperative visit or if the research coordinator is not available on site the day of the subject's appointment, the research coordinator will

attempt to contact the patient by phone, mail or electronically using REDCap, to obtain the outcomes data.

Noncompliance
All patients will be evaluated based on an intention-to-treat analysis. If there is noncompliance to the medicine home taper course indicating cross-over from the treatment arm to the control arm, the overall dose of glucocorticoid will be noted, and patients will be analyzed in their original randomization arm.

Unmasking
Unmasking of the treatment arm will occur should emergency medical services be required within the first 6 days after surgery and emergency personnel need to access a full medicine list for the study patient.

Research Locations
Research will be conducted at the following locations:

Vanderbilt University Medical Center
1211 Medical Center Drive, Nashville, TN 37232

Vanderbilt Health Belle Meade
6002 Highway 100, Nashville, TN 37205

Vanderbilt Orthopaedics Franklin
206 Bedford Way, Franklin, TN 37064

Vanderbilt Surgery Center Franklin
225 Bedford Way, Franklin, TN 37064

Vanderbilt Orthopaedics Lebanon Clinic
1616 West Main St, Suite. 300
Lebanon, TN 37087

Vanderbilt Wilson County Surgery Center
1401 West Baddour Pkwy
Lebanon, TN 37087

Vanderbilt Wilson County Hospital - Operating Suite
1411 West Baddour Pkwy, Suite 1427
Lebanon, TN 37087

Vanderbilt Orthopaedics Hendersonville
128 North Anderson Lane
Hendersonville, TN 37075

7.0 Risks

Side effects that can come from taking Dexamethasone or Methylprednisolone:

- upset stomach
- stomach irritation
- vomiting
- headache

- dizziness
- insomnia
- restlessness
- depression
- anxiety
- acne
- increased hair growth
- easy bruising
- irregular or absent menstrual periods
- skin rash
- swollen face, lower legs, or ankles
- vision problems
- cold or infection that lasts a long time
- muscle weakness
- black or tarry stool

Breach of Confidentiality Risk:

Because patient data is being collected there is a slight risk of a breach of confidentiality. During this study every attempt will be made to keep the patient's protected health information (PHI) private. Most study data will be maintained in a Vanderbilt REDCap database. Vanderbilt Redcap is a secure, web-based application for building and managing online databases. The data obtained and stored in Redcap will only be accessible by research personnel. Any data sent to non-key study personnel for statistical analysis will be de-identified (dates will be shifted using a Redcap feature). Project team members listed as Key Study Personnel with existing electronic health record (EHR) system access rights may also be granted use of REDCap Clinical Data Interoperability Services (CDIS) tools. These tools are designed to enable transfer of relevant study-related data from the Vanderbilt Research Derivative and/or directly from the EHR into REDCap. Any physical study forms (ex. consent documents, surveys) will be kept in a locked cabinet in the principal investigator's office]. All study data will be maintained for 6 years following study completion. Following this 6-year period, the Redcap database will be archived, and all physical study forms will be disposed of in shred-it confidentiality bins.

Benefits

We hope to determine if post-operative range of motion can be improved by peri-operative use of Dexamethasone.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

All adverse events related to this study (breach of confidentiality or drug adverse event) should be reported to the principal investigator immediately. The principal investigator will then ensure prompt reporting to the IRB based on policy number III.L.

9.0 Study Withdrawal/Discontinuation

Participant Withdrawal

Participation in this study is voluntary. If at any time a study participant wishes to be withdrawn from the study, they may do so by contacting their treating physician, the principal investigator or the research coordinator and letting them know they withdraw their consent. The date in which the participant withdraws their consent will be noted in their study file.

Safety Monitor

The Principal Investigator will designate a Safety Monitor for this study. The Safety Monitor will not be involved in the study work and will work independently of the Principal Investigator. The Safety Monitor will be provided reports by the statistician every 6 months, from first subject enrollment, and make a determination on the continuance of the study based on reports of adverse events and protocol deviations.

10.0 Statistical Considerations

Sample Size Justification

Prior studies suggest Flexion/extension arc after intra-articular fracture ~105°. Difference suggested by prior retrospective study with dexamethasone shows potential improvement (δ) of 27° (avg post-operative AROM 132.5°). Conservatively, will attempt to see an improvement of 25° (δ). Average standard deviation from literature of post-operative intra-articular elbow fractures range of motion is 17° (σ). A total of 22 patients are needed (11 treatment and 11 control) to be able to reject the null hypothesis with 90% power and $\alpha = 0.05$. Assuming a 20% loss to follow-up based on prior studies[9] (~10%) + non-compliance of six-day home taper course. As we are stratifying our treatment and control groups based on fracture type, we will need 18 patients in each treatment arm for each fracture and 18 patients in each control arm.

Statistical Analysis

a. Primary analysis
    i. Intention-to-treat
    ii. Baseline characteristics between treatment arms will be compared using univariate descriptive statistics.
    iii. Primary end-point (range of motion: continuous variable) → Univariate analysis of unmatched, interval variable with two groups assuming non-normal distribution: Mann-Whitney U Test will be performed.

iv. Secondary end-points that are dichotomous (infection, revision surgery, heterotopic ossification, and other complication) will be analyzed with a chi-square or Fisher's exact test where the assumptions for a chi-square test are not met.
v. Secondary end-points that are nominal or ordinal (Pain score, DASH score) will be analyzed using a Mann-Whitney U Test.

b. Subgroup analysis
   i. Analysis will be performed based on fracture type and stratification will make comparison possible.
   ii. Multivariate analysis using linear regression for the interval variable (range of motion) will be performed based on:
      1. Age <65 vs Age >65
      2. Mechanism of injury (High-energy vs. Low-energy)
      3. Treatment type
      4. Time from injury to surgery

11.0 Privacy/Confidentiality Issues

During this study every attempt will be made to keep the patient's protected health information (PHI) private. Most study data will be maintained in a Vanderbilt REDCap database. Vanderbilt Redcap is a secure, web-based application for building and managing online databases. The data obtained and stored in Redcap will only be accessible by research personnel. Any data sent to non-key study personnel for statistical analysis will be de-identified (dates will be shifted using a Redcap feature). Project team members listed as Key Study Personnel with existing electronic health record (EHR) system access rights may also be granted use of REDCap Clinical Data Interoperability Services (CDIS) tools. These tools are designed to enable transfer of relevant study-related data from the Vanderbilt Research Derivative and/or directly from the EHR into REDCap. The Research Derivative is a database of clinical and related data derived from the Vanderbilt University Medical Center's (VUMC) clinical systems and restructured for research. Data is repurposed from VUMC's enterprise data warehouse, which includes data from StarPanel, VPIMS, and ORMIS (Operating Room Management Information System), EPIC, Medipac, and HEO among others. The medical record number and other person identifiers are preserved within the database. Data types include reimbursement codes, clinical notes and documentation, nursing records, medication data, laboratory data, encounter and visit data, among others. Output may include structured data points, such as ICD 9 or 10 codes and encounter dates, semi-structured data such as laboratory tests and results, or unstructured data such as physician progress reports. The database is maintained by the Office of Research Informatics under the direction of Paul Harris, Ph.D. Any physical study forms (ex. consent documents, surveys) will be kept in a locked cabinet in the principal investigator's office]. All study data will be maintained for 6 years following study

completion. Following this 6-year period, the Redcap database will be archived, and all physical study forms will be disposed of in shred-it confidentiality bins.

12.0 Follow-up and Record Retention

The duration of this study will last until we have enrolled and completed follow-up on 144 participants. Based on historical frequency, expected study period to accrue the expected sample size will be 2-3 years. All study data will be maintained for 6 years following study completion. Following this 6-year period, the Redcap database will be archived, and all physical study forms will be disposed of in shred-it confidentiality bins.

13.0 References

1. Chen H, Liu G, Wu L. Complications of Treating Terrible Triad Injury of the Elbow: A Systematic Review. *PLoS ONE*. 2014;9(5). doi:10.1371/journal.pone.0097476
2. Kodde IF, van Rijn J, van den Bekerom MPJ, Eygendaal D. Surgical treatment of post-traumatic elbow stiffness: a systematic review. *J Shoulder Elbow Surg*. 2013;22(4):574-580. doi:10.1016/j.jse.2012.11.010
3. Morrey BF, Askew LJ, Chao EY. A biomechanical study of normal functional elbow motion. *J Bone Joint Surg Am*. 1981;63(6):872-877.
4. Wahl EP, Lampley AJ, Chen A, Adams SB, Nettles DL, Richard MJ. Inflammatory cytokines and matrix metalloproteinases in the synovial fluid after intra-articular elbow fracture. *J Shoulder Elbow Surg*. 2020;29(4):736-742. doi:10.1016/j.jse.2019.09.024
5. Desai MJ, Matson AP, Ruch DS, Leversedge FJ, Aldridge JM, Richard MJ. Perioperative Glucocorticoid Administration Improves Elbow Motion in Terrible Triad Injuries. *J Hand Surg*. 2017;42(1):41-46. doi:10.1016/j.jhsa.2016.11.011
6. Kaneguchi A, Ozawa J, Yamaoka K. Anti-inflammatory Drug Dexamethasone Treatment During the Remobilization Period Improves Range of Motion in a Rat Knee Model of Joint Contracture. *Inflammation*. 2018;41(4):1409-1423. doi:10.1007/s10753-018-0788-5
7. Wu Y, Lu X, Ma Y, et al. Perioperative multiple low-dose Dexamethasones improves postoperative clinical outcomes after Total knee arthroplasty. *BMC Musculoskelet Disord*. 2018;19(1):428. doi:10.1186/s12891-018-2359-1
8. Xu H, Zhang S, Xie J, Lei Y, Cao G, Pei F. Multiple Doses of Perioperative Dexamethasone Further Improve Clinical Outcomes After Total Knee Arthroplasty: A Prospective, Randomized, Controlled Study. *J Arthroplasty*. 2018;33(11):3448-3454. doi:10.1016/j.arth.2018.06.031
9. Pugh DMW, Wild LM, Schemitsch EH, King GJW, McKee MD. Standard surgical protocol to treat elbow dislocations with radial head and coronoid fractures. *J Bone Joint Surg Am*. 2004;86(6):1122-1130. doi:10.2106/00004623-200406000-00002