GENERAL INFORMATION

- The Effect on Wrist Range of Motion with Perioperative Glucocorticoid Administration in the Treatment of Adult Distal Radius Fractures: A Randomized Controlled Trial
- PI: C. Liam Dwyer, MD
- Co-I: L. Christopher Grandizio DO, Joel Klena MD, Steven Goldberg MD, Jove Graham PhD
- 100 N Academy Ave
- Danville, PA 17822
- (570) 271-6541
- v1.1, 16 May 2019

OBJECTIVES

The purpose of our investigation is to compare functional outcome measures and range of motion for patients receiving glucocorticoid (GC) injections versus those not receiving GCs for the treatment of DRFs. We hypothesize that patients who receive GC will have improved ROM and functional outcome measures compared to patients who do not receive GC. In addition, we aim to determine if there is a difference in rates of complications and postoperative pain control between the GC and non-GC groups. In order to accomplish our purpose and aims, we plan to conduct a prospective, randomized, controlled investigation.

BACKGROUND AND RATIONALE

Distal radius fractures (DRF) are among the most common fractures in the upper extremity. They can occur both as high energy injuries or as a result of low energy falls, typically as fragility fractures in elderly, osteoporotic patients. Treatment options include both operative and non-operative management. In addition to non-operative management for stable, nondisplaced fractures, open reduction, internal fixation (ORIF) with volar plate (VP) fixation has gained popularity as a treatment option for displaced fractures and fractures with intra-articular involvement. While outcomes for both closed treatment and ORIF have been good, complications related to both digital and wrist stiffness do occur.

Recent authors have found the perioperative administration of glucocorticoids (GC) have improved range of motion after operative treatment of terrible triad injuries for the elbow (DESAI). In addition, there is some evidence that GC administration can aid in postoperative pain control after hip and knee surgery. It is currently unknown if administration of GCs can improve range of motion (ROM) or functional outcomes in patients with DRFs.

PROCEDURES

Research Design

- In order to accomplish our purpose and aims, we will conduct a prospective, randomized, non-blinded study to determine if there is a difference in 1) ROM, 2) functional outcomes, and 3) complications associated with the administration of GC in the treatment of DRFs.

Study Population

- Target Population and Inclusion/ Exclusion Criteria:
    - Target population: Patients undergoing surgery for a distal radius fracture
    - Approximately 100 patients in two groups totaling 200 Geisinger subjects
- Inclusion
    - Patients ≥ 18 years of age
    - Patients undergoing ORIF with VP fixation of an acute, isolated DRF
        - with or without associated distal ulna fracture
        - with or without associated carpal tunnel release

- Exclusion
    - Worker's compensation patient
    - Non-operatively treated fractures
    - Open fractures
    - Preoperative neurovascular injury
    - Coexisting fractures or injuries
    - Diabetes mellitus
    - Allergy or contraindication to GCs
    - Associated non-orthopedic injury that would prohibit the administration of GCs
    - Patients currently incarcerated
    - Pregnant patients

Participant Enrollment

- The PI or a member of the IRB-approved study team will consent patients prior to surgery. A total of 200 patients will be enrolled in the study, 100 in each group.

Recruitment and Screening Procedures

- The investigating surgeons on the study team will identify potential subjects in their clinics. Patients who fit the criteria will be approached by the physician investigators, research coordinators, and/or research assistants during a typical clinic visit or evaluation prior to procedure and be asked to participate in the study. If they agree to learn more about the study, a study team member will review the informed consent form in order to consent the patient, obtain authorization to access/use their PHI, and to enroll them in the study. The patient will sign and date the form after all of their questions have been satisfactorily answered by the study team.

Detailed Study Procedures

- Consent and randomization will occur during the initial clinic visit with the surgeon. Qualifying subjects will be randomized into one of two groups prior to their treatment. The surgeon will not be blinded to either the treatment arm or the group that the patient is randomized into.
- An exception to the consent / randomization process on the initial clinic visit with the surgeon may occur in cases where the determination to proceed with operative treatment

of the DRF does not take place during the initial visit. If it is determined that non-operative management of the DRF is unsatisfactory or if the patient needs additional time to consider operative vs nonoperative treatment, the treating surgeon may elect to introduce the consent / randomization process at the follow-up visit approximately one week later. Observation of DRFs at risk for re-displacement with follow-up radiographs in one week is part of routine clinical practice and is not unique to this research protocol. At the follow-up visit approximately one week later, the patient can then choose to consent for the investigation and will be randomized into one of the two groups (GCs or non-GCs).

- On the day that the patient is consented for the study, they will complete the following assessments in clinic. All of these questionnaires are already a part of our routine collection of functional outcome measures for all patients seen in our clinic.
  1. PROMIS Upper Extremity- Short Form 7a
  2. PROMIS Self-Efficacy for Managing Symptoms- Short Form 8a
  3. PROMIS Pain Interference- Short Form 8A
  4. VAS Pain Scale
  5. QuickDASH

- On the day of surgery, all qualifying patients in the surgery arm of the study will undergo ORIF of their DRF as part of the routine care for each surgeon. The participating surgeon will perform the ORIF (with or without carpal tunnel release) in accordance with their standard practice. Patients will be placed in a short arm splint in accordance with each surgeon's standard practice. In the event that the surgeon determines that there is instability at the distal radio-ulnar joint, the surgeon may elect to utilize a long arm splint. All patients will receive discharge instructions and orders based on the surgeon's standard practice.
- Any complication will be recorded. All postoperative care other than the medications prescribed at the time of discharge and GC medications for the study will be in accordance with each surgeon's standard practice.
- At each of the follow-up visits for patients in both arms, patients will complete the following functional outcome measures, which are already collected as part of our routine clinical practice:
  1. PROMIS Upper Extremity- Short Form 7a
  2. VAS Pain Scale
  3. QuickDASH

- Subjects will participate in the study for approximately 12 months—from initial recruitment to end of participation.
- This study will be completed in approximately 24 months. The end of the study is the last visit of the last subject, or end of collection of data from the patient's electronic health record. Patients may attend additional clinic visits at each surgeon's discretion.
- Patients who meet inclusion criteria will undergo a selection process, and if they choose to participate will be randomized into one of two groups. The randomization scheme will

be created with the use of an internet-based randomization website (https://www.randomizer.org).

Study Arms

ARM 1: GC group

a. Preoperative
    i. Pre-surgery visit
        1. Outcomes
            a. PROMIS SF v1.0 Pain Interference 8a
            b. PROMIS SF v1.0 Self-Efficacy Manage Symptoms
            c. QuickDASH
            d. PROMIS Upper Extremity Short Form 7a
            e. VAS Pain
b. Intraoperative
    i. Single intraoperative dose of 10 mg intravenous dexamethasone
c. Postoperative
    i. A 6-day oral methylprednisolone (oral GC) taper course. The oral GC taper course begins on the day of surgery and includes 24mg on day 1, 20mg on day 2, 16mg on day 3, 12mg on day 4, 8mg on day 5, and 4mg on day 6
    ii. Standard postoperative protocol (note- this postoperative protocol is already part of our retinue clinical practice after operative treatment of DRF):
        1. Day of surgery
            a. ORIF DRF
            b. Short arm splint
        2. 2-week postoperative visit
            a. Removeable wrist brace
            b. Wrist radiographs
            c. Occupational therapy visit to work on digital, wrist and elbow ROM. Standardized measurements which are already obtained as part of our routine clinical practice for wrist ROM, digital ROM and bilateral grip strength.
            d. Functional outcomes measures
                i. QuickDASH
                ii. PROMIS Upper Extremity Short Form 7a
                iii. VAS Pain
        3. 6-week postoperative visit
            a. Discontinue removeable wrist brace
            b. Wrist radiographs
            c. Occupational therapy visit to work on digital, wrist and elbow ROM. Standardized measurements which are

already obtained as part of our routine clinical practice for wrist ROM, digital ROM and bilateral grip strength.

d. Functional outcome measures
    i. QuickDASH
    ii. PROMIS Upper Extremity Short Form 7a
    iii. VAS Pain

4. 3, 6 and 12-month post op visit
    a. Wrist radiographs
    b. Occupational therapy visit to work on digital, wrist and elbow ROM. Standardized measurements which are already obtained as part of our routine clinical practice for wrist ROM, digital ROM and bilateral grip strength.
    c. Functional outcome measures
        i. QuickDASH
        ii. PROMIS Upper Extremity Short Form 7a
        iii. VAS Pain

2. Control (non-GC) group
    a. Intraoperative
        i. No GC administration
    b. Postoperative
        i. As above, but without GC administration

- At the conclusion of the study, the EMR will be reviewed and any instances of unscheduled healthcare contact (email, MyGeisinger messages, telephone calls, unscheduled clinic visits, ED visits) will be recorded and analyzed for cause.
- All surgeons participating in the study will adhere to the randomization, treatment, and follow-up protocol. There will be 4 participating sites within the Geisinger system (GMC, GMC Woodbine, Geisinger Shamokin Hospital, Bloomsburg Hospital) who will participate in this research project.

Study Time and Events Table

Study Procedures	Visit pre-surgery	Visit Day of Surgery	Postoperative follow-up visits at Woodbine Ortho (2w, 6w, 3m, 6m, 1y)
Prescreen	X		
Provide Info Sheet	X		
Review Inclusion/Exclusion	X	X	
Demographics, medical history, habits, historical diagnoses	X		
Consent of Patient	X		
Randomization	X		
AE / Complication Reporting			X
Surgery		X	
Dexamethasone administered intra-op via IV*		X	
Post-op oral steroid taper*		X	
Occupational therapy visit			X
Wrist radiograph			X
Outcome measures (QuickDASH, PROMIS Pain Interference, PROMIS Self-Efficacy Manage Symptoms, PROMIS Upper Extremity, VAS Pain)/ examination assessment recorded	X		
Outcome measures (QuickDASH, PROMIS Upper Extremity, VAS Pain)/ examination assessment recorded			X

* GC group only

- The primary endpoint is to determine if there is a statistically significant difference with regards to functional outcome scores and ROM for patients treated with and without GCs
- Secondary Endpoints:
  - Differences in complications
  - Differences in time to union and rate of non-union
  - Differences in rates of unscheduled healthcare contact

DATA MANAGEMENT

Data Management Procedures and Confidentiality

- A member of the IRB-approved Geisinger study team will perform a manual chart review for data points not captured during the BC data pull. A member of the IRB approved study team will randomly assign study ID numbers in order to protect the identity of the subject. After the dataset has been de-identified, an IRB-approved study team member will forward the completed dataset to Jove Graham, PhD for analysis. All study data will be kept in GHS maintained username/password-protected computer files and hard copy data will be double locked and accessible only to the study investigators in the locked office of the Study Coordinator. Only group-level information without personal identifiers will be included when presenting results or submitting manuscripts for publication.
- Records of data generated in the course of the study will be kept indefinitely and may be used for future research purposes.
- No PHI will be shared outside of the IRB approved study staff.

Data Analysis/ Statistical Considerations:

- Based on the results of a previous study comparing operative treatments for ORIF of DRF, grip strength was chosen as the primary outcome parameter and used to estimate the required sample size. Seventeen patients were needed in each group to show a difference in grip strength of 20% with a power of 85% in a 2- sided test at the 5% significance level (KOPYLOV).
- In another study, QuickDASH was the primary subjective outcome measure. The level of significance was set at $P < .05$; to achieve a 90% power to find a difference of 10 points, which is the minimal clinical important difference, 49 patients were required for each group (WILLIKSEN).
- Based on these prior investigations, we plan to enroll 100 patients in each of the two arms, for a total of approximately 200 patients.
- All data analysis will be performed by the study team, led by the co-investigator Jove Graham, PhD. Descriptive statistics will be generated to describe the baseline and pre-surgery characteristics of patients in the two groups. Although it is assumed that randomization should balance any confounding variables among the study arms, this assumption will be checked by comparing all baseline characteristics and looking for significant differences so that any potential confounders can be addressed in the

subsequent analyses of the aims via stratification or regression adjustment. All analysis will be performed using SAS 9.4 (SAS Institute, Cary, NC) and R 3.0.3 (R Foundation, Vienna, Austria) statistical software, with differences considered statistically significant at the $p<0.05$ level.

- The following data will be collected from the EMR:
  1. PHI elements (will not be included in final dataset)
     - Medical Record Number (MRN)
     - Name
     - Date of birth
     - Visit dates
       - Date(s) and information related to of admission, surgery, and discharge
       - Date(s) and information related to clinic visits
  2. Patient Demographics (Age, gender, weight, height, Body Mass Index (BMI))
  3. Medical History
     - Diabetes Mellitus
     - Insulin use
     - Chronic kidney disease
     - Narcotic use history
     - Hand dominance
     - Inflammatory or Rheumatoid Arthritis
  4. Complications / Adverse Events
     - Wound Hematoma
     - Tendon rupture
     - Nonunion
     - Malunion
     - Delayed union
     - Superficial wound infection (defined as any prescription for post-op antibiotics)
     - Wound complications
     - Deep infection (defined as need for surgical irrigation and debridement)
     - Readmission
  5. Unscheduled healthcare contact and reason for contact
     - Phone calls
     - Emails
     - MyGeisinger Messages
     - Unscheduled clinic visits
     - ED visits

EXPECTED RISKS/ BENEFITS

Potential Risks

- There are some risks related to steroids, but most of these are related to long-term use. The short-term usage of steroids is usually safe. These medications are commonly used in surgery to help with postoperative nausea, pain and swelling. They are also used to treat inflammation related to injuries or trauma.
    - Side effects include increased blood sugar levels, changes in appetite, changes in mood, dizziness, trouble sleeping and allergic reactions.
- Any time information is collected for a study there is a small risk of breach of confidentiality or accidental disclosure of PHI (i.e. MRNs, dates). However, this risk is not greater than the risk that already exists in clinical settings when handling medical data.
- Clinical adverse events (AEs) will be monitored throughout the study. All AEs will be reported to the institutional review board (IRB) according to IRB policy. The date and time of onset and outcome, course, intensity, action taken, and causality to study treatment will be assessed by the study PI. A subject's AEs will be recorded and reported from the signing of the informed consent form to end of study period.

Benefits

- There are no direct benefits from enrolling in this study. We anticipate this study will benefit society and future research.

Informed Consent

- The investigator will provide for the protection of the subjects by following all applicable regulations. The informed consent form will be submitted to the IRB for review and approval. Prior to having any study procedures performed, the patient will be asked to read and then sign the informed consent form if they agree to participate in the study. The subject will receive a copy of the signed/dated informed consent form for their records. The original copy of the informed consent form will be scanned into the subject's EMR and the hardcopy will be filed in the subject's study binder. The rights and welfare of the subjects will not be affected. We are requesting to observe and record variables that are normally collected and entered into the patient's EMR in the course of standard clinical care. The purpose of recording data for this prospective study (in addition to the EMR) is simply to ensure that discrete, standardized format (since some variables, while stored in the EMR, may appear in physician notes as free text).
- A partial waiver of HIPAA authorization is being requested for this study. A waiver is necessary for the research to be practically conducted because the research team much review the patient's PHI to determine eligibility. The research team would be unaware of potential eligible patients without reviewing that patient's relevant medical information. If the patient does not meet eligibility criteria, they will not be approached to partake in the study. While PHI is being requested, it is the minimal amount necessary to ensure patients are eligible based on the inclusion criteria.

Protection of Human Subjects Against Risks

- The investigator will provide for the protection of the subjects by following all applicable regulations. Anticipated risks in this study are minimal. This study will not affect patient

care or access to care. The major risk to human subjects in this study is the accidental disclosure of PHI. In this regard, the assignment of a coded test ID number to each individual participant and the protocol of providing only the necessary associated clinical information to the remainder of the research team mitigate this risk.

- All study data will be kept in Geisinger Health System maintained username/password-protected computer files and hard copy data will be double locked and accessible only to the study investigators. Only group-level information without personal identifiers will be included when presenting results or submitting manuscripts for publication.

PUBLICATION PLAN

- We plan to prepare and submit the results of this study for presentation at national meetings and in peer-reviewed journals.

BIBLIOGRAPHY

Thompson PW, Taylor J, Dawson A. The annual incidence and seasonal variation of fractures of the distal radius in men and women over 25 years in Dorset, UK. Injury. 2004 May 1;35(5):462-6.

Arora R, Lutz M, Hennerbichler A, Krappinger D, Espen D, Gabl M. Complications following internal fixation of unstable distal radius fracture with a palmar locking-plate. Journal of orthopaedic trauma. 2007 May 1;21(5):316-22.

Desai MJ, Matson AP, Ruch DS, Leversedge FJ, Aldridge III JM, Richard MJ. Perioperative glucocorticoid administration improves elbow motion in terrible triad injuries. The Journal of hand surgery. 2017 Jan 1;42(1):41-6.

Lunn TH, Kehlet H. Perioperative glucocorticoids in hip and knee surgery–benefit vs. harm? A review of randomized clinical trials. Acta Anaesthesiologica Scandinavica. 2013 Aug;57(7):823-34.

Kopylov P, Runnqvist K, Jonsson K, Aspenberg P. Norian SRS versus external fixation in redisplaced distal radial fractures. A ran- domized study in 40 patients. Acta Orthop Scand. 1999;70(1):1e5.

Williksen JH, Husby T, Hellund JC, Kvernmo HD, Rosales C, Frihagen F. External fixation and adjuvant pins versus volar locking plate fixation in unstable distal radius fractures: a randomized, controlled study with a 5-year follow-up. The Journal of hand surgery. 2015 Jul 1;40(7):1333-40.