Title

Low-Dose Radiation Therapy for Heterotopic Ossification Prophylaxis in Distal Humerus Fractures

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Purpose:
To determine the effectiveness of 500 cGy dose of radiation therapy vs. an untreated group in the prophylactic treatment of heterotopic ossification in distal humerus fractures

Hypothesis:
Use of low-dose radiation therapy at a single 500 cGy dose postoperatively will decrease the incidence and severity of heterotopic ossification in distal humerus fractures without increasing the non-union rate.

Background/Scientific review:
Heterotropic ossification is the formation of ectopic lamellar bone in the soft tissues. The process is thought to occur through local and distal recruitment osteoprogenitor cells especially mesenchymal stem cells which lead to HO formation based on local microenvironmental factors including activation of the BMP-mediated pathways.[1] There are several risk factors associated with HO development such as central nervous system injury, thermal burn, hip arthroplasty, acetabular fractures, and elbow fractures; HO is also seen with certain arthropathies and genetic conditions e.g. ankylosing spondylitis, seronegative arthropathies, diffuse idiopathic skeletal hyperostosis (DISH), and fibrodysplasia ossificans progressiva.[1,2] In elbow fractures the prevalence of HO is around 40%, and of those that develop HO, 20% experience a clinically relevant decrease in elbow range of motion with a flexion-extension arc of <100°. In a study by Foruria, et al. of 89 patients with a distal humerus fracture without associated proximal radius or ulna fracture that underwent surgical treatment with ORIF, 42% developed HO and the HO in these patients was associated with significantly less extension and a limited flexion-extension arc but was not associated with a change in supination or pronation.[3] Abrams, et al. looked at the development of HO after elbow fracture fixation in 89 pts including 20 distal humerus fractures and found that distal humeral fractures were more likely to have higher grade of HO, have more compromised functional outcomes, and require return to the OR more often for capsular release with HO resection at a rate of 25%.[4] Prophylactic treatment for HO is most commonly achieved through the use of NSAIDs such as indomethacin and radiation therapy. Both modalities have the risk of nonunion of fracture and radiation therapy has additional risks such as delayed wound healing, soft tissue contracture, and the theoretical risk of malignancy although no cases of malignancy after prophylactic radiation have been reported to date.[1,2] Radiation therapy in the prevention of HO has been well studied in the hip with low-dose radiation being established as an effective does and 700cGy as the most commonly used dose.[5] Radiation therapy in the prevention of HO at the elbow is not as well studied and existing studies have commonly used a dose of 700cGy. One study looked at the use of radiation therapy in combination of patients being treated acutely for elbow trauma and patients being treated for HO after previous elbow trauma, and the study found that 3 of the 36 patients developed new HO and found an occurrence of 2 nonunion with the majority treated with 700cGy but 2 pts received 600cGy.[6] Heyd, et al. present a case series of 9 patients that underwent surgical excision of clinically significant HO at the elbow and received radiation therapy of 2 doses of 500cGy (5), 1 dose of 600 cGy (3), or 1 dose of 700 cGy (1); at a mean follow up of 7.7 no patients had recurrence of HO and 8 of 9 showed clinical improvement.[7] A study of 11 patients that underwent ORIF for fracture-dislocation of the elbow and single dose radiation therapy of 700 cGy within 72 hours postoperatively, and 3 patients (27%) developed radiographic evidence of HO while 10 patients (91%) had no functional

limitations and 100% of patients completely healed there fracture without complications at average follow up of 12 months (9-24 months). 3 of the 11 patients had distal humerus fractures and none of them had radiographic evidence of HO or functional limitation.[8] A recent multicenter randomized control trial of patients with intraarticular distal humerus fractures or fracture-dislocation of the elbow with proximal ulna and/or radius fracture randomized patients to either receive a single dose of 700cGy within 72 hours postop or receive nothing for HO prophylaxis. Although, HO occurrence in the 21 patients in the treatment group vs the 24 in the control group (33% vs 54%), the rate of nonunion was higher in the treatment group (38% vs 4%) resulting in termination of the study.[9] Several studies has demonstrated the efficacy and safety of radiation therapy in the prophylactic treatment of HO in elbow, but the study by Hamid questions the use of a 700 cGy dose because of the rate of nonunion observed. Thus we hypothesize that a dose of 500 cGy will be adequate in the elbow HO prevention as there is smaller treatment area compared to the hip where 700 cGy is an effective dose, and that this dose will note result in an increased rate of nonunion.

Study Design:

Prospective, randomized, un-blinded study taking place at the University of Louisville Hospital. Patients will be presented the consent form and enrolled preoperatively at the University of Louisville Hospital. Patients will be randomized into one of two groups via a standard blocked randomization table. Patients who consent will be randomized into either treatment group or the control group, i.e. no medical or radiation therapy heterotopic ossification prophylaxis.

Inclusion Criteria:

1. Patient has a distal humerus fracture
2. Patient's age is greater than or equal to 18

Exclusion Criteria:

1. Patient has a concomitant proximal ulna and/or proximal radius fracture
2. Patient requires external fixation of the elbow
3. Patient has a concomitant central nervous system injury or GCS <13 at time of surgery
4. Patient has quadriplegia or paraplegia
5. Patient requires intubation upon admission or for >4 hours during admission for nonsurgical purposes
6. Patient has concomitant soft tissue damage in the affected elbow that cannot be appropriately closed within 72 hours of surgery
7. Patient has a burn affecting greater than or equal to 20% of the total body surface area or on the affected eblow
8. Patient has pre-existing heterotopic ossification in the affected elbow

Sample Size:

Power analysis has been performed demonstrating 45 patients per treatment group would provide an alpha of 0.05 and a beta of 0.80.

Radiation Therapy Protocol:

External Beam Radiation

1. Localization, Positioning and Immobilization:
A volumetric planning CT study will be required to define region of interest for each patient. Each patient will be positioned in an immobilization device in the treatment position on a flat table. Contiguous CT slices of 1-3 mm will be obtained to include the entire treatment volume and organs at risk.

2. Treatment planning:
Treatment planning will be performed using conventional radiation techniques with either standard 2-dimensional radiotherapy or 3-dimensional radiotherapy. Typically, AP-PA fields should be used and calculated to midplane. No Less than 6 MV energy photons will be used, and no bolus is placed on the skin. The field covers the entire joint, the antecubital fossa and the olecranon process. A strip of skin at the antecubital area is generally shielded, but is not an absolute requirement for this study.

3. Treatments:
A dose of 500cGy will be delivered in 1 fraction to the isocenter. Radiation should be administered no later than 72 hours postoperatively.

Adverse Events

1. Radiation Toxicities

1. The CTEP Common Terminology Criteria for Adverse Events (CTCAE v4.0) will be used. Standard radiation related toxicities are expected. Toxicity will be defined as acute (<3 months from completion), subacute (3-12 months) and late (>12 months). Standard consent forms for extremity radiation will be used for informed consent. Reversible or permanent alopecia, skin pigmentation, and local edema are expected side effects of radiation therapy.

2. Adverse Event Reporting: Adverse events (AE) and serious adverse events (SAE) will be reported in a timely manner through the appropriate channels. The investigator will assess and determine whether the event is related to the study treatment and assign the following category (possible, probable, definite). Please see below for definitions of each.

-AE: Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. (CTEP, NCI guidelines: Adverse event reporting requirements)

-**SAE**: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in the following: death, life-threatening adverse experience, inpatient hospitalization, a persistent or significant disability, or a cognitive anomaly.

- SAE will include any event leading to the following:

· Death;

· A life-threatening adverse experience;

· Inpatient hospitalization or prolongation of existing hospitalization;

· A persistent or significant disability/incapacity;

· A congenital anomaly/birth defect.

Reporting of Adverse Events

All AEs, regardless of severity and whether or not they occurred during the study treatment or within 21 days following the last treatment, are to be documented by the Investigator appropriately, including date of onset, severity, action taken, outcome, and relationship to study drug. Adverse events occurring between the time of signing informed consent to the time of the first dose will NOT be captured as AEs unless the AE is a direct result of a study-specific procedure or results in death from an event other than PD.

In the case of an SAE, the Investigator must notify the Institutional Review Board and the Co-Chairman of the Data Safety Monitoring Committee within 24 hours of becoming aware of the event.

Subject Registration and Data Collection

8.1.1 Subject registration: The informed consent process must be completed prior to initiation of any study required activities. Registration into the study will occur when the following criteria are met:

-Patient meets all inclusion and no exclusion eligibility criteria

-Patient provides written informed consent

8.1.2 Patient study identification numbers will be assigned in ascending order. This patient identifier will be recorded in the Subject Enrollment Log and placed on the header of all case report forms and study related materials to identify the subject. Subject data will be recorded in a secure location and database in the Clinical Trials Office.

8.2.1 Data Collection: Data will be collected according to the protocol requirements for

all patients registered to the trial, including early termination and patients deemed ineligible.

8.3.1 The study chair and project team will collect monthly reports of the study project
and accrual.

DSMC Review

An independent committee, called the Data Safety and Monitoring Committee (DSMC) will review the progress of the study and monitor subjects' accrual, serious adverse events and unexpected events. Through this process the DSMC is also assessing the continuing validity and scientific merit of the trial. The DSMC members are from the Study Chair's Institution, the Brown Cancer Center, University of Louisville. Members on the committee view themselves as representing the interests of the study patients and not that of the institution. The DSMC makes written reports summarizing their findings at each review.

The DSMC meets quarterly, or more frequently if requested by the Principal Investigator.
The study statistician will provide the DSMC interim analysis reports determined by statistical methods noted in this protocol.

Ethical and Regulatory Considerations

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice.

- Informed Consent

- The principles of informed consent are described by Federal regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office of protection from Research Risks Reports; protection of Human Subjects (Code of Federal regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

- Institutional Review; This study must be approved by an appropriate institutional review committee as defined by Federal regulatory Guidelines (Ref. Federal Register Vol. 46, No 17, January 27, 1981, part 56) and the

Office for protection from Research Risks Reports; Protection of Human Subjects (Code of Federal regulations 45, CFR 46).

Data Collection:
Age, Date of Birth, Sex, GCS score, Weight, Height, BMI, PreOp Evaluation Date, PreOp Diagnoses, Date of Procedure, Type of Procedure, Side of Procedure, Operative MD, operative description (approach used, type of implant(s) used), Estimated intra-operative blood loss, Operative time, incidence of postop transfusion, date of discharge, Hospitalization days, Total length of follow-up, postop complications, Pre-operative elbow range of motion, post-operative and follow up elbow range of motion, Pre-operative radiographs, post-operative and follow up appointment radiographs

Outcome Measurements:
Presence of heterotopic ossification on plain radiographs taken in the anteroposterior and lateral planes at six weeks, three months, and six months quantified using the classification systems described by Brooker, et al. and Hastings and Graham.
Clinical function measured using the Mayo Elbow Performance Score and elbow range of motion in flexion and extension, and in supination and pronation assessed at six weeks, three months, and six months. Additionally, patient health status using the 36-Item Short Form Survey (SF-36) will be assessed at six weeks, three months, six months, and one year. Fracture healing also assessed on aforementioned plain films and intervals, the interval check for nonunion will be performed every 6 months.
Complications – need for revision surgery, surgery for excision of HO or capsule release, and nonunion.

Data Management:
Once consent has been obtained pre-operatively, a separate data sheet (paper) will be utilized for each patient. The sheet will be stored in a ring-binder along with the consents in the senior investigators office, which is kept locked. Only persons involved in data collection will have access to PHI.

Procedures for Maintaining Confidentiality:
A breach of confidentiality and/or privacy is a risk of this study. To prevent this, all collected data will be stored electronically in password-protected files to protect patient identity and information. All information will be collected and reviewed by the research team only. Data will be maintained on a password-protected computer that will be accessible only to the study team. Investigators and/or the Study Coordinator will assign each subject a Research ID# and keep a password protected Excel spreadsheet linking Research ID# and date of birth in a separate password protected computer so that the "key" is separated from the research database. As soon as all data have been collected and there is no further need to return to a subject's medical record, the Excel key linking the date of birth to research ID numbers will be destroyed.

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