University of Maryland, Shock Trauma Center
Department of Orthopaedics

External Beam Radiotherapy as Prophylaxis for Heterotopic Ossification After Surgical Fixation of Acetabular Fractures: a Prospective, Randomized Feasibility Study

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List of General Abbreviations/Terminology

HO	Heterotopic Ossification
CRF	Case Review Form
IRB	Institutional Review Board
LAR	Legally Authorized Representative
PI	Principal Investigator
XRT	External Beam Radiation
STC	University of Maryland R Adams Cowley Shock Trauma Center
RCT	Randomized Controlled Trial

PROTOCOL SUMMARY

Title	External Beam Radiotherapy as Prophylaxis for Heterotopic Ossification After Surgical Fixation of Acetabular Fractures: a Prospective, Randomized Feasibility Study
Short Title	HO Prophylaxis
Type of Study	Pilot RCT study
Primary Objective	To determine severe HO formation (Brooker class III-IV) between XRT versus no XRT.
Sample Size	100
Diagnosis and Main Inclusion Criteria	Patients 18+ with an acetabular fracture requiring surgical intervention amenable to XRT.
Length of Follow-up	3 months post-operative

Introduction

Heterotopic ossification (HO) is a common complication after surgical fixation of acetabular fractures, with incidence reported as high as 90%. HO can be a debilitating complication and surgical excision for more severe cases carries a high complication rate. Numerous strategies have been employed to prevent HO formation, but results are often conflicting, and the optimal treatment strategy remains controversial.

The most common interventions used to prevent HO formation are oral administration of indomethacin or single-dose external beam irradiation therapy (XRT). Despite the common use of indomethacin and observational data to support its use, more recent randomized controlled trials (RCTs) have failed to demonstrate any significant reduction in the incidence of severe HO when patients were administered 6 weeks of indomethacin versus placebo. In contrast, XRT has been shown to be effective against HO formation but there remain concerns surrounding the cost and potential long-term effects of XRT. Other authors have described debridement of the gluteus minimus muscle as a primary form of prevention, but the severe HO rate in the largest series of this approach (12%) is higher than that of numerous series that administered XRT as prophylaxis (1-5%).

Given the high incidence of HO, the impact of severe HO on outcomes, and the controversy regarding prophylaxis methods, there remains a need for randomized controlled trials (RCT) to determine optimal strategies for HO prophylaxis. The primary aim of this study is to assess the effect of XRT in preventing severe HO after acetabular surgery.

Study Objectives

This pilot RCT will determine the effect of external beam radiation (XRT) on preventing severe heterotopic ossification (HO) after acetabular surgery.

Study Design

This prospective pilot RCT will enroll 100 patients 18 years and older with an acetabular fracture requiring surgical intervention. Patients will be randomized to receive XRT or no XRT post-operatively.

Methods

Setting

Patients will be enrolled at the University of Maryland STC and Emery University. Each clinical site will require local IRB approval. The PI at STC will provide oversight and guidance for the trial and regulatory requirements.

Eligibility Criteria

The inclusion criteria are:

1. Ages 18+
2. Acute acetabular fracture
3. Indicated for surgical fixation via a posterior or combined anterior and posterior approach

The exclusion criteria are:

1. Contraindication to radiotherapy, such as history of cancer/RT
2. Patient is getting an acute total hip arthroplasty at the time of fixation of the acetabular fracture.
3. Patient is currently pregnant or breastfeeding.
4. Patient is likely to have difficulty returning for post-operative follow-ups (i.e. homeless, incarceration)
5. Patient does not speak English.

Recruitment Strategy, Patient Screening, and Consent

All patients 18 years or older presenting to the hospital with an acute acetabular fracture indicated for surgical fixation will be screened for eligibility by local research staff in close coordination with surgeons and relevant medical staff. Research staff will review the daily orthopaedic trauma census and confirm eligibility by reviewing patient medical records. The PI will be available to answer questions regarding study eligibility. When the PI is not available, any questions will be forwarded to available medical personnel or designated research team member. Surgeons must be willing to participate and have their patients enrolled. Once eligibility has been confirmed, the informed consent process will be completed by research staff with surgeon assistance if possible. Patients will be approached in person by study staff prior to surgery or immediately after about potential participation in the study, whichever is most feasible following determination of eligibility.

Legally Authorized Representative Consent: This study will include vulnerable patients incapable to give informed consent. For these individuals we will obtain consent from a legal authorized representative (LAR). The choice of LAR will follow standard procedures. The following with be approached in this order of priority:

- Legal guardian
- Proxy (health care agent) named in an advance directive or durable power of attorney for health care;
- Family member or other surrogate identified by the state law on health care decisions.

Patients, family members, and/or authorized representatives will be included in all study-related discussions and at the time of consent, they will be reminded that all participation is voluntary and the alternative is not to participate. During this consent process, we will review the study and consent forms, and use an Evaluation to Sign Consent Form asking questions based on the study to assess their full understanding and comprehension of what we are asking.

If/when the patient recovers and is able to provide consent for him or herself, we will repeat the consent process with the patient to ensure he or she is still willing to participate.

Randomization: Once consented, eligible patients will be randomized by study staff to XRT versus control. Randomization will be a 50/50 chance, like the flip of a coin. Randomization will occur in REDCap.

Trial Interventions: Both arms will receive gluteus minimus debridement in the OR, which is considered the standard of care. If randomized to the treatment group, patients that undergo surgical fixation of an acetabular fracture via a posterior or combined anterior and posterior approach will undergo a single fraction of external beam radiotherapy to the surgical site within 72 hours of surgery. This treatment is currently the standard procedure performed for all patients who undergo a posterior or combined approach. The control treatment arm will only include gluteus minimus debridement in the OR and will not receive XRT.

Data Collection

After obtaining informed consent, research personnel will record the baseline data on the study CRFs. They will obtain this information directly from the participant or proxy, from the participant's medical chart, and the participant's treating surgeon. Data collected will include patient demographics and injury characteristics, operative details, imaging, medical history, and complications (i.e. reoperation). 3 month post operative x-rays will be reviewed to assess HO formation. Additionally, any serious adverse events will be recorded. All data will be de-identified and recorded in REDCap.

Sample Size

We will enroll 100 patients across all sites. Enrolling 100 patients will give the study 80% power to detect an 88% reduction in the odds of severe HO using a two-sided alpha level of 0.05. The calculation assumes the rate of severe HO in the control group would be 20%.

Statistical Analysis

The primary analysis will follow the intention to treat principle, evaluating patients according to the group to which they were randomly assigned. To guard against any imbalances in randomization, the effect of XRT on our study outcomes using logistic regression models will be assessed, which will include a treatment indicator and adjusted for head injury, mechanical ventilation, acetabular hip dislocation, and associated fracture pattern. An as-treated sensitivity analysis will also be performed, in which patients will be evaluated according to the HO prophylaxis they received regardless of the treatment assignment. All analyses will be completed using R Version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Data Management

All eCRFs will be completed by designated, trained site personnel. Research personnel will enter data as detailed on the CRFs into the secure University of Maryland, Baltimore REDCap system. Clinical site personnel will have a unique login and password for the system and will be able to view and modify data for participants recruited at their local site. The University of Maryland, Baltimore staff will monitor and oversee all data as it is collected across both sites, ensuring there is no missing, implausible, or inconsistent data. The trial will be conducted following GCP guidelines.

Ethics

The University of Maryland, Baltimore, and Emory University will obtain ethics/IRB approval prior to commencement of participant enrollment.

Confidentiality

Information about trial participants will be kept confidential and will be managed in accordance with the below rules:

1) All trial-related information will be stored securely.
2) All trial participant information will be stored in locked file cabinets and accessible only to site research personnel.
3) All paper and electronic CRFs will be identified only by a coded participant number.
4) All databases will be password protected.

If a participant revokes authorization to collect or use personal health information, the clinical site retains the ability to use all information collected prior to the revocation of participant authorization.

Protocol Amendments

Any amendments to the study protocol which may affect the conduct of the study, the potential safety of, or benefits to participants (e.g., changes to the objectives, design, sample size, or procedures) will require a formal amendment to the protocol. Any protocol amendments will be approved by the Principal Investigator and may require approval by all applicable ethics committees and regulatory agencies. Clinical sites will also be required to submit amendment requests to their ethics committee to obtain approval for the amendment. Administrative changes (e.g., minor corrections or clarifications that have no effect on the way the trial is conducted) will not need to undergo a formal amendment process.

Safety Reporting and Monitoring

Safety Plan

The safety plan for participants in this study is based on clinical experience with the trial interventions in completed and ongoing studies. The trial period during which AEs must be reported begins after the patient has consented and enrolled in the study and continues until the end of the participant follow-up period at their first post-operative visit. AEs recorded during this period will be followed through to resolution, or until the event is deemed chronic or stable.

The anticipated important safety risks are outlined below. Several measures will be taken to ensure the safety of participants, including the use of inclusion and exclusion criteria and close monitoring of participants. Administration of the study procedures will be performed in a setting in which participants are closely monitored for potential adverse events, and there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence in a participant administered medicinal product and which does not necessarily have a causal relationship with this treatment. It can therefore include any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product or other protocol-imposed intervention.

Serious Adverse Event (SAE)

An AE should be classified as a SAE if any of the following criteria are met:

- It results in death (e.g., the AE causes or leads to death).
- It is life-threatening (e.g., the AE, in the view of the investigator, places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (e.g., the AE results in substantial disruption of the participant's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational medical product.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above).

Unexpected Serious Adverse Event

Any SAE that meets all the following criteria:

- Is unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol and informed consent document and the characteristics of the patients eligible for the trial.
- Is related or possibly related to treatment/procedures under trial; possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the trial procedures or treatments.
- Suggests that participation in the trial may place participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems may not classify as adverse events. To be considered an adverse event, the unanticipated problem must be an untoward or unfavorable medical occurrence in a trial participant.

Reporting AEs and Unanticipated Events

Local Investigator Reporting

The local investigator is responsible for ensuring that all AEs including SAEs that are observed or collected during the study are reported to the appropriate local IRBs and the Methods Center, in accordance with applicable regulatory requirements.

Event Reporting Timelines
Local site investigators will report SAEs within the following timelines:
- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded and reported to the sponsor within 24 hours of awareness.
- SAEs, other than deaths and immediately life-threatening events, will be reported within 72 hours of site awareness.

SAE information must be submitted no later than 30 calendar days from the time the local investigator becomes aware of the event.

Clinical sites will follow local procedures for submitting safety reports and follow-up information to their local ethics committee.