The Use of External Beam Radiation Therapy for Heterotopic Ossification Prophylaxis After Surgical Fixation of Acetabular Fractures: A Randomized Controlled Trial

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OBJECTIVES: To determine the effect of external beam radiation (XRT) on preventing severe heterotopic ossification (HO) after acetabular surgery.

METHODS:

Design: Randomized controlled trial.

Setting: Two level I academic trauma centers.

Patient Selection Criteria: Patients with an acetabular fracture (OTA/AO type 62) surgically treated through a posterior or combined anterior and posterior approach.

Outcome Measures and Comparisons: Radiographic HO was determined using Brooker Classification at the last follow-up. The primary outcome was severe HO (Brooker classes III–IV). The secondary outcome was any HO (Brooker classes I–IV). The incidence of radiographic HO was compared between patients who did and did not undergo postoperative XRT. The results were analyzed in both an intention-to-treat (randomized to XRT) and as-treated (received XRT) basis.

RESULTS: Severe HO occurred in 3 of 54 (6%) patients randomized to XRT and 9 of 50 (18%) patients randomized to no XRT (odds ratio 0.24, 95% confidence interval, 0.05 to 0.94; $P = 0.05$). Any HO occurred in 10 (19%) patients assigned to XRT and 17 (34%) patients in the no XRT control group (odds ratio 0.39; 95% confidence interval, 0.13 to 1.05; $P = 0.07$).

CONCLUSIONS: The findings of this dual-center randomized controlled trial suggest that XRT after acetabular surgery significantly reduced the odds of severe HO compared with patients who did not receive XRT. These results can help guide shared decision making between surgeons and patients regarding the use of XRT for HO prophylaxis.

KEY WORDS: heterotopic ossification, external beam radiation, Kocher–Langenbeck

LEVEL OF EVIDENCE: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

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INTRODUCTION

Heterotopic ossification (HO) is a common complication after surgical fixation of acetabular fractures, with incidence reported as high as 90%.[1–4] HO can be a debilitating complication and surgical excision for more severe cases carries a high complication rate.[5] Numerous strategies have been used 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).[1,6–10] Despite the common use of indomethacin and observational data to support its use,[9,10] 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.[11–13] 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.[1,2,4,7,8,14–17] Other authors have described debridement of the gluteus minimus muscle as a primary form of prevention,[18] but the severe HO rate in the largest series of this approach (12%)[19] is higher

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than that of numerous series that administered XRT as prophylaxis (1%–5%).[2,4,7,8,16,17,19] In addition, the study by Chen et al[20] was a direct comparison of gluteus medius debridement versus preservation and showed no difference in incidence of postoperative HO.

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

METHODS

Trial Design

This RCT was conducted at 2 urban level I academic trauma centers. The study protocol was approved by institutional review boards at both participating sites, and all study participants provided written informed consent. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Eligibility Criteria

All patients aged 18 years or older with displaced operative acetabular fractures (OTA type 62) who presented to the hospital, either through direct center referral or through referral from outside medical centers, were identified and screened for eligibility. The protocol included patients treated with internal fixation through a posterior (eg, Kocher–Langenbeck, Gibson), combined anterior and posterior, or extensile exposure. Excluded were patients who were unable to speak or read English, had an operative intervention performed through an isolated anterior approach, acute total hip arthroplasty performed at time of index surgery, or had contraindications to XRT (eg, pregnancy, active connective tissue disorder, or prior radiation to overlapping site that would preclude further radiation). Patients with bilateral injuries were eligible, but only the most severe fracture (in the opinion of the treating surgeon) was included.

Surgical Protocol

Surgical fixation was performed before the random allocation of the prophylaxis strategy to prevent differential intraoperative decision making. Preoperative prophylactic antibiotics were administered to all patients within 60 minutes of surgical incision. If no contraindication existed, tranexamic acid (TXA) was given intravenously (1 gram). A posterior approach to the hip was performed in standard fashion through an interval (eg, Kocher–Langenbeck vs. Gibson) at the discretion of the surgeon. Either before fracture reduction and fixation or after the instrumentation, debridement of the devitalized gluteus minimus muscle was performed in both study groups. Closed suction drainage was used at the discretion of the treating surgeon.

Randomization and Masking

Informed consent was obtained either before or after surgery. Participants were randomly assigned to XRT or no XRT in a 1:1 ratio. Randomization was performed by a central computerized system with variable blocks. To ensure prognostic balance, randomization was stratified based on associated vs. elementary fracture pattern and by participating site. The study participants and surgeons were aware of study group allocation postoperatively to allow for the arrangement of XRT as needed.

Intervention

Patients randomized to the XRT treatment arm received postoperative XRT in the form of a single dose (7–8 gray) of radiation delivered to the surgical site within 72 hours of surgery. Patients randomized to no XRT did not receive any HO prophylaxis.

Study Outcomes

The primary outcome was severe HO formation, defined as a Brooker class III or IV, given this is the most clinically significant form of HO. The secondary outcome was any HO formation, defined as Brooker classes I–IV. HO measurements were performed using the Brooker classification with the Moed et al modification.[21,22] Postoperative radiographs at the last follow-up after 6 weeks were reviewed for evidence of HO. Patients with radiographic follow-up $<$ 6 weeks were excluded, consistent with the literature.[19] A fellowship trained orthopaedic traumatologist reviewer, masked to the study group allocation, performed all radiographic assessments.

Statistical Analysis

It was determined that enrolling 100 patients would give the study 80% power to detect an 88% reduction in the odds of severe HO using a 2-sided alpha level of 0.05. The calculation assumes the rate of severe HO in the control group would be 20%.

The primary analysis followed 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 was assessed on the study outcomes using logistic regression models, which included a treatment indicator and adjusted for head injury, mechanical ventilation, associated hip dislocation, and associated fracture pattern, as prespecified. An as-treated sensitivity analysis in which patients were evaluated according to the HO prophylaxis they received regardless of the treatment assignment was performed. All analyses were completed using R Version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The study population enrolled and randomized 117 patients in this trial (Fig. 1). Of these 117 patients, 3 patients had early conversion ($<$6 weeks) to total hip arthroplasty and 10 patients were lost to follow-up (Fig. 1) and were not available for analysis. The mean follow-up time for the remaining 104 patients was 16 weeks (range 6–104 weeks). The mean patient age was 36 $\pm$ 12 years and 72% were men (Table 1). There were 54 (52%) elementary fracture patterns and 50 (48%) associated fracture patterns. Ninety-three patients

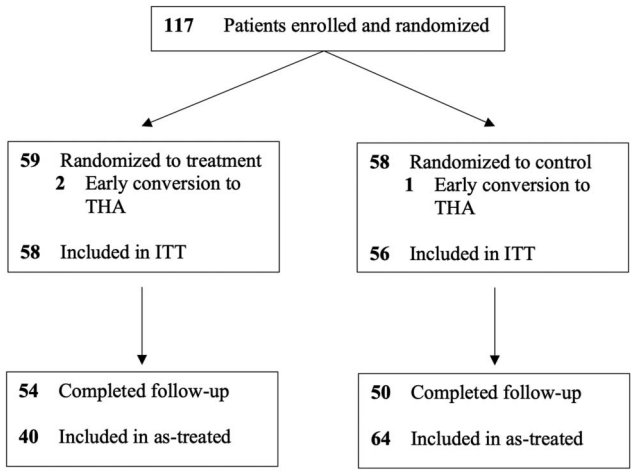

FIGURE 1. Flow diagram. ITT, intention to treat; THA, total hip arthroplasty.

(89%) had a Kocher–Langenbeck surgical approach, 11 patients (11%) had a combined anterior and posterior approach, and no patients were treated with an extensile approach.

On an intention-to-treat basis (randomized to XRT or no XRT), severe HO (Brooker classes III–IV) occurred in 3 of 54 (6%) patients assigned to XRT and 9 of 50 (18%) patients assigned to the no XRT control group (odds ratio (OR) 0.24, 95% confidence interval (CI) 0.05 to 0.94; $P = 0.05$) (Table 2). In the as-treated analysis (received XRT or did not receive XRT), severe HO occurred in 1 of 40 (3%) patients who received XRT compared with 11 of 64 (17%) patients who did not receive XRT (OR 0.11, 95% CI, 0.01–0.64; $P = 0.04$).

Any HO (Brooker classes I–IV) occurred in 10 of 54 patients (19%) assigned to XRT and 17 of 50 patients (34%) assigned to the control group (OR 0.39, 95% CI, 0.15–1.01; $P = 0.06$). In the as-treated analysis, any HO occurred in 7 of 40 patients (18%) who received XRT compared with 20 of 64 patients (31%) who did not receive XRT (OR 0.39, 95% CI, 0.13–1.05; $P = 0.07$).

TABLE 2. Study Outcomes

Outcome	XRT	No XRT	Odds Ratio (95% CI)*	*P*
Severe HO (%)				
ITT	3/54 (6)	9/50 (18)	0.24 (0.05–0.94)	0.05
As-treated	1/40 (3)	11/64 (17)	0.11 (0.01–0.64)	0.04
Any HO (%)				
ITT	10/54 (19)	17/50 (34)	0.39 (0.15–1.01)	0.06
As-treated	7/40 (18)	20/64 (31)	0.39 (0.13–1.05)	0.07

*Logistic regression models adjusted for head injury, mechanical ventilation, acetabular hip dislocation, and associated fracture pattern.
ITT, intention to treat.

DISCUSSION

This multicenter RCT demonstrated postoperative XRT protected against severe HO (Brooker III–IV) among patients who underwent surgical fixation of an acetabular fracture through a posterior or combined anterior and posterior surgical approach. A similar magnitude of protection was observed against any HO (Brooker I–IV) with XRT but failed to reach statistical significance. The findings provide high-quality evidence to the continued debate on HO prophylactic practices after acetabular surgery.[23]

There are currently 5 RCTs on HO prophylaxis in this patient population.[11–13,15,16] Three of these studies did not include XRT as a treatment arm,[11–13] and the latter 2 are by the same senior author and institution with some redundant

TABLE 1. Patient Characteristics

Characteristic	Overall, N = 104	XRT, N = 54	No XRT, N = 50
Age, mean (SD)	36 (12)	35 (11)	37 (13)
Male	75 (72%)	35 (65%)	40 (80%)
Race (%)			
African American	65 (62)	36 (67)	29 (58)
White/Caucasian	35 (34)	16 (30)	19 (38)
Asian	2 (2)	1 (2)	1 (2)
Other	2 (2)	1 (2)	1 (2)
Hispanic ethnicity	3 (3)	1 (2)	2 (4)
Head injury	21 (20)	11 (20)	10 (20)
Acetabular fracture dislocation	50 (48)	25 (46)	25 (50)
Associated fracture pattern	50 (48)	26 (48)	24 (48)
Surgical approach (%)			
Kocher–Langenbeck	93 (89)	49 (91)	44 (88)
Combined anterior and posterior	11 (11)	5 (9)	6 (12)
Trochanteric osteotomy	6 (6)	3 (6)	3 (6)
Gluteus minimus muscle debridement	100 (96)	51 (94)	49 (98)
NSAIDs for pain management	38 (37)	19 (35)	19 (38)
Closed suction drain at wound closure	42 (40)	22 (41)	20 (40)
Tranexamic acid used	34 (33)	14 (26)	20 (40)
Mechanical ventilation	29 (28)	12 (22)	17 (34)

data.[15,16] In the original article by Moore et al,[15] XRT was compared with indomethacin as HO prophylaxis interventions, and no control group was included. In the subsequent article by Burd et al,[16] the authors added 4 years of data to the original study, and included a small subset of patients "that were too unstable medically to be transported to radiation or because indomethacin treatment had not been given or had been terminated prematurely" as a control group. In both studies, treatment arms were determined by patient medical record number, and there was a disparity in groups between ratio of elementary to associated fracture patterns. These drawbacks, particularly the lack of comparison between XRT and an appropriate control group, make any comparison between these data and the current study findings difficult.

This study found that patients who received XRT had a 3% incidence of severe HO, and this confirms previous findings in the literature from retrospective studies that demonstrated severe HO rates of 1%–5% when XRT was given for prophylaxis.[2,7,8,17] In addition, the patients in this study who did not receive XRT had a severe HO rate of 17%, which also confirms previous findings of severe HO rates of 12%–32% when no XRT was given.[2,4,7,8,19] It has been described that devitalized gluteus minimus muscle can be a nidus for HO.[18] This devitalized tissue is often routinely debrided, which was part of the study protocol. The retrospective study by Davis et al[8] demonstrated a severe HO rate of 32% with gluteus minimus debridement only compared with 4% with gluteus minimus debridement with XRT ($P = 0.02$). This retrospective study most closely resembles the current study treatment groups and the current overall findings are aligned in that the addition of XRT significantly reduces the incidence of severe HO after acetabular surgery.

The most common drawbacks cited against the use of XRT are risks of infection, wound complications, and the theoretical risk of XRT-induced sarcoma. Although some data do exist that have illustrated a higher rate of noninfectious wound complications after XRT,[24] the largest cohort on this subject includes 361 patients who received XRT for a 10-year period and did not find any increased risk of wound problems and reported a deep infection rate of 6%, which aligns with the literature.[25]

The risk of single-dose XRT as a direct cause of sarcoma seems anecdotal because there remains a baseline risk in the general population. The most robust study on this topic is a matched case–control study on approximately 4000 patients who received XRT as HO prophylaxis after either acetabular surgery or total hip replacement for a 19-year period.[26] The study demonstrated no increased risk of malignancy in patients who were treated with XRT for HO prophylaxis compared with those who were not. In addition, of the patients who did develop a malignancy, none were in the radiation field. It is worth considering that if XRT works to decrease severe HO, there are risks of not using it. These risks include poor hip function because of decreased range of motion and potential complications during HO resection surgery that, in rare cases, could even include death.

The primary strength of this study is that it is a multicenter RCT. Randomization is important given the number of confounders associated with HO, which cannot be adequately controlled in an observational study. The outcome measure of severe HO is likely clinically meaningful and relatively straightforward to evaluate. The treatment arms mimic the most common current treatments in North America,[23] including that both treatment arms received gluteus medius debridement. Finally, the study was adequately powered and enrolled relatively quickly, which limits the chance of clinical practice changes during the trial.

A limitation of this study is the 14-patient crossover from the XRT treatment arm to no XRT. The most common reason for crossover was patients did not want to be physically moved postoperatively to receive XRT and declined transport. Despite this crossover, the study data illustrated a clinically and statistically significant reduction in severe HO on both an intention-to-treat and as-treated bases. Although the sample size was adequately powered, the relatively few number of study events warrants consideration. Although the study is multicenter, it is only 2 centers, which might limit the generalizability of the findings.

CONCLUSIONS

The results of this multicenter RCT suggest that XRT after acetabular surgery significantly reduces the odds of severe HO. These findings may help guide shared decision making between surgeons and patients regarding the use of XRT as HO prophylaxis.

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