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SYMPOSIUM: FRACTURES OF THE ACETABULUM

Is Preoperative Radiation Therapy as Effective as Postoperative Radiation Therapy for Heterotopic Ossification Prevention in Acetabular Fractures?

Michael T. Archdeacon MD, MSE, Albert d'Heurle MD, Nicole Nemeth MD, Bradley Budde MD

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Abstract

Background Prophylactic approaches to prevent heterotopic ossification after acetabular fracture surgery have included indomethacin and/or single-dose external beam radiation therapy administered after surgery. Although preoperative radiation has been used for heterotopic ossification prophylaxis in the THA population, to our knowledge, no studies have compared preoperative and postoperative radiation therapy in the acetabular fracture population.

Questions/purposes We determined whether heterotopic ossification frequency and severity were different between patients with acetabular fracture treated with prophylactic radiation therapy preoperatively and postoperatively.

Methods Between January 2002 and December 2009, we treated 320 patients with a Kocher-Langenbeck approach for acetabular fractures, of whom 50 (34%) were treated with radiation therapy preoperatively and 96 (66%) postoperatively. Thirty-four (68%) and 71 (74%), respectively, had 6-month radiographs available for review and were included. For hospital logistical reasons, patients who underwent operative treatment on a Friday or Saturday received radiation therapy preoperatively, and all others received it postoperatively. The treatment groups were comparable in terms of most demographic parameters, injury severity, and fracture patterns. Six-month postoperative radiographs were reviewed and graded according to Brooker. Followup ranged from 6 to 93 months and 6 to 97 months for the preoperative and postoperative groups, respectively. Post hoc power analysis showed our study was powered to detect a difference of 22% or more between patients with severe heterotopic ossification. Sample size calculations showed 915 subjects would be needed to detect a 5% relative difference in severe heterotopic ossification status between groups.

Results We detected no difference in heterotopic ossification frequency between the preoperative (eight of 36, 22%) and postoperative (19 of 71, 27%) groups ($p = 0.609$). There was also no difference in heterotopic ossification severity between groups ($p = 0.666$). Two of 36 (6%) in the preoperative group and three of 71 (4%) in the postoperative group developed clinically significant

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.
This work was performed at the University of Cincinnati Medical Center, Cincinnati, OH, USA.

M. T. Archdeacon (✉), A. d'Heurle
Department of Orthopaedic Surgery, University of Cincinnati, PO Box 670212, Cincinnati, OH 45267-0212, USA
e-mail: michael.archdeacon@uc.edu; archdemt@uc.edu

N. Nemeth
Department of Orthopaedic Surgery, Palo Alto Medical Foundation–Mountain View, Mountain View, CA, USA

B. Budde
Department of Anesthesiology, Rush University Medical Center, Chicago, IL, USA

Grade III heterotopic ossification. No patients developed Grade IV heterotopic ossification.

Conclusions We found no difference in heterotopic ossification frequency or severity when comparing preoperative and postoperative radiation therapy. However, given the relatively low frequency of heterotopic ossification in this population, in particular the frequency of severe or symptomatic heterotopic ossification, the possibility of a Type II error must be considered. Larger, prospective studies are required to confirm our no-difference finding, but insofar as the result in this fracture population mirrors that of the THA population, unless our finding is disproven, we believe radiation therapy can be given either before or after surgery, as dictated by the clinical scenario.

Level of Evidence Level III, therapeutic study. See Instructions for Authors for a complete description of levels of evidence.

Introduction

Heterotopic ossification is a well-documented complication after operative treatment of acetabular fractures and may be seen on plain radiographs as early as 3 to 6 weeks after the injury but is maximized between 6 and 12 weeks [1, 4, 8, 10, 15, 16, 20–24, 33].

Well-established risk factors for the development of heterotopic ossification include posterior or extensile approaches to the acetabulum, T-type acetabular fractures, a high Injury Severity Score, a delay to surgery, a closed head injury, male sex, and trauma to the chest or abdomen [4, 8, 10, 15, 24, 29, 32, 33]. The most common forms of heterotopic ossification prophylaxis include indomethacin and/or single-dose external beam radiation therapy given postoperatively [6, 7]. In these studies, patients were educated on both treatment modalities and chose an option based on their perception of the associated risks and benefits.

Given that the local stimuli for the initiation of heterotopic ossification likely occurs at the time of injury, a reasonable hypothesis would be that prophylaxis may be more effective if given closer to the time of injury rather than immediately postoperatively [25]. Preoperative external beam radiation has been used for heterotopic ossification prophylaxis in the THA population [11, 13, 18, 19, 31]. However, the literature provides little insight regarding the efficacy of preoperative radiation therapy for heterotopic ossification in patients with acetabular fracture. Thus, as an initial step, we compared preoperative and postoperative single-dose external beam radiation for heterotopic ossification prophylaxis in terms of the frequency and severity of heterotopic ossification in patients with acetabular fractures treated via a Kocher-Langenbeck approach.

Patients and Methods

Between January 2002 and December 2009, we treated 320 patients with a Kocher-Langenbeck approach for acetabular fractures, of whom 50 (34%) were treated with radiation therapy preoperatively and 96 (66%) postoperatively. Of those, 34 (68%) and 71 (74%), respectively, had 6-month radiographs available for review and were included ($p = 0.568$).

Radiation therapy was administered after consultation by the radiation oncology service. A single-fraction dose was delivered using 6 to 10 mV ranging from 700 to 800 cGy [7]. For hospital logistical reasons, patients who underwent operative treatment on a Friday or Saturday received radiation therapy preoperatively, and for all others, radiation therapy was delivered postoperatively.

The preoperative group had 34 patients (29 males, five females) with 36 acetabular fractures and had a mean age of 48 ± 14 years (range, 17–79 years) (Table 1). The postoperative group had 71 patients (53 males, 18 females) with 71 acetabular fractures and had a mean age of 41 ± 14 years (range, 24–76 years; $p = 0.026$ compared to the preoperative group). The treatment groups were comparable in terms of most demographic elements, injury severity, and relevant surgical parameters. We found no differences between groups in terms of associated injuries, including hip dislocation; sciatic nerve palsy; the presence of other skeletal, abdominal, thoracic, and neurologic injuries; and Injury Severity Score (Table 2). Time to surgery, blood loss, and operative time likewise were not different between groups (Table 3).

All patients were treated in a standard fashion for our institution with immediate closed reduction of hip dislocations in the emergency department followed by balanced skeletal traction. The acetabular fracture was treated as soon as the patient was cleared for surgery. All patients underwent a Kocher-Langenbeck approach to the acetabulum in the lateral decubitus position. In all cases, devitalized gluteus minimus muscle was resected as recommended by Routt and Swiontkowski [29] to reduce the risk for heterotopic ossification.

Demographic, injury, and treatment data were abstracted from the prospectively collected acetabular fracture database. The literature supports maturation of heterotopic ossification within 6 to 12 weeks from injury/surgery [1, 9, 14, 21–24, 26]; therefore, radiographic review at 6 months postsurgery was performed to assess heterotopic ossification as described by Brooker et al. [5]. Two independent investigators (NN, BB) evaluated the radiographs and assigned a Brooker grade. In cases where the evaluators were in disagreement as to the Brooker grade, the senior author (MTA) adjudicated. The development of heterotopic ossification was further analyzed based on clinical

Table 1. Patient demographics

Variable	Preoperative radiation therapy group	Postoperative radiation therapy group	p value
Number of patients/fractures	34/36	71/71	
Mean age (years)	48 (range, 17–79)	41 (range, 24–76)	0.026
Sex (number of fractures)			0.309
Male	30 (83%)	53 (75%)	
Female	6 (17%)	18 (25%)	
Fracture type (number of fractures)			0.680
Posterior wall	16 (44%)	37 (52%)	
Posterior column	1 (3%)	3 (4%)	
Posterior column/posterior wall	4 (11%)	5 (7%)	
Both columns	0 (0%)	1 (1%)	
Transverse posterior wall	10 (28%)	20 (28%)	
Transverse	2 (6%)	1 (1%)	
T-type	2 (6%)	4 (6%)	
Anterior column posterior hemitransverse	1 (3%)	0 (0%)	
Mechanism of injury (number of fractures)			0.932
Motor vehicle collision	28 (78%)	56 (79%)	
High fall (> 10 feet [3 m])	3 (8%)	5 (7%)	
Motorcycle collision	2 (6%)	3 (4%)	
Low fall (< 10 feet [3 m])	3 (8%)	3 (4%)	
Industrial crush injury	0 (0%)	2 (3%)	
Pedestrian versus automobile	0 (0%)	1 (1%)	
Other	0 (0%)	1 (1%)	

Table 2. Associated injuries

Variable	Preoperative radiation therapy group (n = 36 fractures)	Postoperative radiation therapy group (n = 71 fractures)	p value
Injuries (number of fractures)			
Hip dislocation	27 (75%)	56 (79%)	0.650
Sciatic nerve palsy	4 (11%)	5 (13%)	1.000
Associated skeletal injuries	22 (61%)	36 (50%)	0.301
Associated abdominal injuries	7 (19%)	5 (7%)	0.318
Associated thoracic injuries	10 (28%)	11 (15%)	0.127
Associated neurologic injuries	1 (3%)	1 (1%)	1.000
Injury Severity Score (points)*	12 ± 9	15 ± 21	0.625
Marginal impaction (number of fractures)	20 (56%)	32 (45%)	0.337
Wall comminution (≥ 3 fragments) (number of fractures)	16 (44%)	31 (44%)	0.988
Femoral head injury (number of fractures)	9 (25%)	21 (30%)	0.618

* Values are expressed as mean ± SD.

insignificance (Grade 0, Grade I, and Grade II) and clinical significance (Grade III and Grade IV) [5, 6, 10, 15, 24, 27].

Statistical comparison using a Student's t-test or chi-square analysis was first used to compare demographic, injury, and treatment variables. A Wilcoxon rank-sum test was performed to compare the Brooker grade between the two groups. Statistical significance was set at p values of less than 0.05 for all analyses. Statistical analysis was performed using SAS® 9 software (SAS Institute, Inc, Cary, NC, USA). A post hoc power analysis showed our

Table 3. Treatment variables

Variable	Preoperative radiation therapy group (n = 36 fractures)			Postoperative radiation therapy group (n = 71 fractures)			p value
	Mean	Median	Range	Mean	Median	Range	
Treatment interval (injury to surgery) (days)	6	5	2–16	4	4	0–14	0.061
Operative blood loss (mL)	614	537	100–1850	669	500	150–2200	0.791
Operative time (hours)	201	195	120–323	201	175	95–552	0.242

Table 4. Distribution of heterotopic ossification development

Variable	Number of fractures		p value
	Preoperative radiation therapy group (n = 36 fractures)	Postoperative radiation therapy group (n = 71 fractures)	
Heterotopic ossification			0.609
No	28 (78%)	52 (73%)	
Yes	8 (22%)	19 (27%)	
Brooker grade			0.666
I	5 (14%)	9 (13%)	
II	1 (3%)	7 (10%)	
III	2 (6%)	3 (4%)	
IV	0 (0%)	0 (0%)	

study was powered to detect a relative difference of 22% or more between the patients with severe heterotopic ossification. Sample size calculations showed that 915 subjects would be needed to detect a 5% relative difference in severe heterotopic ossification status between groups.

Results

With the numbers available, the frequency of heterotopic ossification was no different between the preoperative group (eight of 36, 22%) and the postoperative group (19 of 71, 27%) ($p = 0.609$) (Table 4).

With the numbers available, the groups likewise were comparable in terms of the severity of heterotopic ossification ($p = 0.666$) (Table 4). Two of 36 (6%) in the preoperative group and three of 71 (4%) in the postoperative group developed clinically significant Grade III heterotopic ossification. No patients in either group developed Grade IV heterotopic ossification.

Discussion

Radiation therapy has been shown to be effective in reducing the risk of developing heterotopic ossification after open reduction and internal fixation of the acetabulum [4, 24]. Radiation therapy is thought to disrupt the mesenchymal stem cells and is most effective if administered within 3 days postoperatively [1–3, 7, 12]. The rationale for this study is based on the premise that prophylaxis may be more effective if given closer to the time of injury rather than immediately postoperatively [25]. In the THA population, preoperative radiation therapy has been safely utilized for heterotopic ossification prophylaxis [11, 19]; however, to our knowledge, this has not been investigated for patients with acetabular fracture. In comparing preoperative radiation therapy to postoperative radiation therapy, we did not observe a difference in the frequency and severity of heterotopic ossification for patients with acetabular fracture.

Several limitations to our study need to be addressed. The study design was retrospective, and so there may have been differences between the study groups. Furthermore, the incidence of heterotopic ossification was evaluated radiographically, not clinically. Also, the mean age between groups was different (preoperative: 48 years; postoperative: 41 years, $p = 0.026$); however, we do not believe that a mean age difference of 7 years has any clinical relevance in this patient population. Potential risk factors for the development of heterotopic ossification include neurologic injury, abdominal and/or thoracic trauma, an elevated Injury Severity Score, delay in operative fixation of the fracture, and extensile or posterior approaches to the acetabulum [4, 8, 10, 15, 16, 20, 21, 24, 33]. While it was not possible to control for all of the heterotopic ossification risk factors, the two groups of patient in our series were similar in terms of sex, mechanism of injury, hip dislocation rate, associated injuries including neurologic injuries, operative time, estimated blood loss, treatment interval, Injury Severity Score, and Glasgow coma scale. An additional consideration concerns the logistical parameters within our system that necessitated preoperative radiation therapy for patients who had acetabular surgery on a Friday or Saturday, and it is possible that these patient groups would be different although they appear similar. Our statistical power was another limitation; given the low rate of heterotopic ossification overall, it would have taken a much larger sample size to detect a difference between the two treatment groups. A post hoc power analysis demonstrated that our study was adequately powered to detect only a 22% relative difference in the development of heterotopic ossification. Given how infrequently clinically severe heterotopic ossification occurs, we believe our study is important, as it can serve as pilot data for future prospective studies. Sample size calculations showed that 915 subjects would be needed to detect a 5% relative difference in severe heterotopic ossification status between groups.

The frequency and severity of heterotopic ossification in our series were similar to those observed in other studies of heterotopic ossification that used postoperative radiation for prophylaxis [1, 24]. Anglen and Moore [1], in a series of 21 patients with acetabular fracture treated surgically followed by postoperative radiation for the prevention of heterotopic ossification, found that six patients (28.6%) went on to develop either Grade I or II heterotopic ossification. Similarly, Moore et al. [24], in a series of 33 patients, found that nine patients (27.3%) developed heterotopic ossification after receiving radiation therapy. Schafer et al. [30], in a series of 44 patients treated with radiation, found that 19 patients (43.2%) developed some form of heterotopic ossification. Providing more relevance to our investigation, Mourad et al. [25] demonstrated in a series of 585 patients with acetabular fractures that patients who received radiation therapy closest to the time of injury had a lower incidence of heterotopic ossification compared to patients whose radiation therapy was delayed.

In the elective hip surgery population, Pellegrini et al. [28] examined the difference between preoperative and postoperative radiation therapy for the prevention of heterotopic ossification after THA. In a cohort of 86 hips, they found 12 of 49 patients (24%) developed heterotopic ossification in the preoperative group versus 10 of 37 patients (27%) in the postoperative group. The radiation dose was delivered either 6.1 hours before surgery or within 51.3 hours after surgery [28]. Lonardi et al. [19] examined just the rate of heterotopic ossification in patients treated with radiation within 16 hours before THA and found the rate of heterotopic ossification to be six of 143 (4.2%). Other studies have found the rate of heterotopic ossification ranges from 5% to 48% in patients irradiated for heterotopic ossification prophylaxis between 4 to 20 hours before THA [11, 13, 18, 31].

Although preoperative radiation therapy has been shown to be safe and effective in the prevention of heterotopic ossification in elective THA procedures [11, 13, 18, 19, 31], there are no reports to our knowledge of this being done in the trauma patient setting. The exact pathophysiology of heterotopic ossification is not completely understood; however, some have theorized that initial traumatic insult is the root cause of the heterotopic bone [17, 24]. Because of this, we believed there might have been some potential advantage to earlier administration of radiation therapy and that preoperative treatment might have been more effective than postoperative radiation in the prevention of heterotopic ossification in patients with trauma. However, in our series, with the numbers available, we found no difference in the frequency or severity of heterotopic ossification between patients who received radiation before surgery versus those who received it after surgery.

In conclusion, we believe that radiation therapy for heterotopic ossification prophylaxis can be given preoperatively or postoperatively, at least until disproven by larger, prospective studies. This recommendation is supported in the THA literature. Additionally, in the trauma setting, preoperative administration may have some theoretical advantages, mainly therapy initiation closer to the time of injury. Finally, although a relatively small study, we believe our data are valuable and can serve as pilot data for larger, prospective studies further investigating preoperative versus postoperative radiation therapy as heterotopic ossification prophylaxis in acetabular fractures.

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