Radiation Therapy for Heterotopic Ossification Prophylaxis Acutely After Elbow Trauma

A Prospective Randomized Study

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Background: Heterotopic ossification around the elbow can result in pain, loss of motion, and impaired function. We hypothesized that a single dose of radiation therapy could be administered safely and acutely after elbow trauma, could decrease the number of elbows that would require surgical excision of heterotopic ossification, and might improve clinical results.

Methods: A prospective randomized study was conducted at three medical centers. Patients with an intra-articular distal humeral fracture or a fracture-dislocation of the elbow with proximal radial and/or ulnar fractures were enrolled. Patients were randomized to receive either single-fraction radiation therapy of 700 cGy immediately postoperatively (within seventytwo hours) or nothing (the control group). Clinical and radiographic assessment was performed at six weeks, three months, and six months postoperatively. All adverse events and complications were documented prospectively.

Results: This study was terminated prior to completion because of an unacceptably high number of adverse events reported in the treatment group. Data were available on forty-five of the forty-eight patients enrolled in this study. When the rate of complications was investigated, a significant difference was detected in the frequency of nonunion between the groups. Of the nine patients who had a nonunion, eight were in the treatment group. The nonunion rate was 38% (eight) of twenty-one patients in the treatment group, which was significantly different from the rate of 4% (one) of twenty-four patients in the control group ($p = 0.007$). There were no significant differences between the groups with regard to the prevalence of heterotopic ossification, postoperative range of motion, or Mayo Elbow Performance Score noted at the time of study termination.

Conclusions: This study demonstrated that postoperative single-fraction radiation therapy, when used acutely after elbow trauma for prophylaxis against heterotopic ossification, may play a role in increasing the rate of nonunion at the site of the fracture or an olecranon osteotomy. The clinical efficacy of radiation therapy could not be determined on the basis of the sample size. Further research is needed to determine the role of limited-field radiation for prophylaxis against heterotopic ossification after elbow trauma.

Level of Evidence: Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.

Heterotopic ossification is a well-recognized complication after elbow trauma. It can result in pain, loss of motion, and impaired function. Although the exact pathogenesis remains unclear, it is believed to result from the inappropriate differentiation of pluripotential mesenchymal cells into osteoblastic stem cells, which leads to the deposition of mature lamellar bone in the periarticular soft tissues[1]. Risk factors associated with heterotopic ossification include genetic predisposition, local tissue trauma, and neurological abnormalities [2,3]. The prevalence of heterotopic ossification of the elbow has been reported to range from 3% in simple elbow dislocations to 89% in patients with both a head injury and elbow trauma[4]. Ilahi et al. found an overall prevalence of 49% in forty-one patients with fractures of the elbow[5]. A retrospective review performed at our institution showed a prevalence of 35% in forty-six patients with intra-articular distal humeral fractures[6]. Ten of those patients required surgical treatment for symptomatic heterotopic ossification.

Treatment of heterotopic ossification about the elbow can be challenging. In severe cases, radical surgical excision of the ossified soft tissues is performed; however, this procedure can be fraught with complications and the results of surgical management remain unclear[7]. Therefore, preventive measures have been utilized with increasing frequency. Stein et al. reported on single-dose radiation therapy to prevent heterotopic ossification after elbow trauma and found it to be safe and effective[8]. Robinson et al. retrospectively reviewed fiftythree patients who received postoperative single-fraction radiation for the prevention of heterotopic ossification after elbow surgery and concluded that it was safe and effective[9]. Despite these encouraging retrospective reports, we were unable to find a prospective randomized study to clearly define the role of radiation therapy in the acute setting after elbow trauma.

The purpose of this prospective randomized study was to determine if single-fraction radiation (700 cGy) is safe and effective when used to prevent heterotopic ossification acutely after elbow trauma. We hypothesized that the radiation therapy could be administered safely, improve clinical results, and perhaps decrease the number of elbows requiring excision of heterotopic ossification.

Materials and Methods

Study Design and Subjects

We conducted a prospective, randomized clinical trial[10]. Patients were enrolled at three major medical centers after approval was obtained from each institutional review board. All patients gave their written informed consent prior to study enrollment. The trial was registered at ClinicalTrials.gov (NCT00991887).

Forty-eight patients were prospectively enrolled from September 2005 to December 2008. The mean age was fortyfour years (range, eighteen to sixty-five years). All patients sustained one of the following injury patterns: (1) an intraarticular distal humeral fracture (Orthopaedic Trauma Association [OTA] classification 13-C1, 13-C2, and 13-C3) or (2) a fracture-dislocation of the elbow with proximal radial and/or ulnar fracture (OTA classification 21-B1, 21-B2, 21-B3, 21-C1, 21-C2, and 21-C3)[11]. No patient declined to participate. Both open and closed injuries were included. Patients were excluded if they had one of the following associated injuries: a head injury (quantified by a Glasgow Coma Scale score of <13 at the time of operative intervention), burns of >20% of the body surface area or involving the operative site, or a spinal cord injury affecting the function of the upper extremities. Patients with open fractures that could not be closed within seventy-two hours of the initial operative intervention were also excluded. Fracture fixation was performed by orthopaedic surgeons with fellowship training in orthopaedic trauma or shoulder and elbow reconstruction. An olecranon osteotomy was performed in fourteen (31%) of the forty-five patients to facilitate exposure of the fracture site.

Study Intervention

Patients were randomly assigned (see below) to receive either radiation therapy (the treatment group) or nothing (the control group) for prophylaxis against heterotopic ossification. For patients allocated to the treatment group, radiation therapy was administered within seventy-two hours after operative fixation of the fracture by a board-certified radiation oncologist. It was given as a single fraction at a dose of 700 cGy at 6-MeV energy photons with use of AP-PA (anteroposteriorposteroanterior) fields calculated to midplane, with a mean window of 12 · 8.2 cm, for all patients[12]. The field covered the entire elbow joint, antecubital fossa, and olecranon process. This protocol has been described previously at other institutions[8,9].

Randomization

Patients were assigned to one of the two groups (treatment or control) by a computer-generated randomization schedule. In order to improve precision in the comparison of treatment means, assignment was in a ratio of 1:1 in a complete block design of ten. Each clinical site was provided with a separate randomization schedule and received a set of sealed, opaque envelopes containing the randomization assignment for each study participant. The treating surgeon and patient were blinded to group assignment until after operative treatment.

Clinical Outcome Measures

Clinical outcome was assessed at six weeks, three months, and six months. The primary clinical outcome was the Mayo Elbow Performance Score (MEPS). This outcome tool is based on a 100-point scale, which measures pain (45 points), stability (10 points), function (25 points), and motion (20 points)[13]. The result was graded on the basis of the MEPS as excellent (‡90 points), good (75 to 89 points), fair (60 to 74 points), and poor (<60 points). Range of motion (flexion, extension, pronation, and supination) was measured at each data collection point.

Radiographic Measures

The radiographic outcomes assessed were the presence of heterotopic ossification and healing of the fracture and the site of the osteotomy (if performed). Plain radiographs in the anteroposterior and lateral planes were made at six weeks, three months, and six months postoperatively. Additional imaging (radiograph or computed tomography scan) was made if deemed necessary by the treating physician or if fracture union was not achieved at six months. The most recent radiographs were used to determine the radiographic outcome. The classification systems described by Brooker et al. and Ilahi et al. were used to quantify the presence of heterotopic ossification radiographically[14,15]. The Brooker classification of heterotopic ossification includes four grades of heterotopic ossification, with grade I indicating heterotopic islands; grade II, heterotopic ossification with >1 cm between opposing bone surfaces; grade III, heterotopic ossification with <1 cm between opposing bone surfaces; and grade IV, joint ankylosis. The more severe grade of the two systems was used as the final grade of the severity of heterotopic ossification, as the Ilahi system is useful for anterior heterotopic ossification classification only. Union was also assessed. A nonunion was defined as a fracture or olecranon osteotomy site that had not healed at six months after the injury and had shown no progressive signs of healing for three months[16]. All radiographs were reviewed by three orthopaedic traumatologists, blinded as to treatment group.

Adverse Events

An adverse event was defined as any adverse change in health or a so-called side effect that occurs in a patient participating in a clinical trial while he or she is receiving the treatment or within a prespecified period of time after treatment has been completed. All adverse events were documented, and the primary investigator was notified. The trial was periodically monitored by an institutional review board-designated safety monitor at least twice a year to ensure protocol compliance and safety of the study.

Statistical Analysis

Data were verified and prepared for analysis by checking for missing information; calculating the range, mean, median, and standard deviation, as appropriate; and comparing with hospital administrative data to identify possible data entry errors.

After correction, there were no missing data for any of the variables of interest. For all analyses, a p value of <0.05 was considered significant. The Fisher exact test and t tests were used for statistical analysis. Additional analyses used binomial logistic regression to control for the influence of radiation therapy on body mass index in the distribution of nonunions, and analysis of variance was used to explore group differences between time to surgery and the formation of heterotopic ossification and nonunion.

Sample Size and Power Analysis

The sample size of the study was based on the projected difference in the rates of heterotopic ossification between the two study groups. A rate of 35% in the nonradiation therapy group was estimated on the basis of previous reports of heterotopic ossification after elbow trauma[5]. It was judged that a reduction in the rate of heterotopic ossification of 60% (to a rate of 15%) would be clinically meaningful. Therefore, assuming a significance level of $p < 0.05$ and a nominal power of 80%, it was estimated that seventy-three patients would be needed per group.

Source of Funding

The Carolinas Medical Center Health Services Foundation and the Orthopaedic Trauma Association provided funding for this study.

Results

This study was terminated prior to completion because of an unacceptably high rate of adverse events being reported in the treatment group. This was identified by the safety monitor at the scheduled review. The radiation treatment group was found to have a significantly higher nonunion rate ($p = 0.007$), and study enrollment was discontinued.

Data were available on forty-five of the forty-eight patients (Fig. 1). Twenty-six patients were allocated to the control group and two were lost to follow-up, leaving twenty-four for

Fig. 1

Diagram showing the flow of participants through each phase of the trial.

analysis. Twenty-two patients were allocated to the radiation therapy group and one was lost to follow-up, leaving twentyone for analysis. The baseline characteristics appeared similar between the control and treatment groups (Table I). The mean duration of follow-up was 7.5 months (range, six to twenty-six months).

	Control Group (N = 24)	Radiation Therapy Group (N = 21)	P Value*
Age† (yr)	45 ± 15	44 ± 17	0.8
Sex‡			
Male	11 (46)	14 (67)	0.2
Female	13 (54)	7 (33)	0.2
Body mass index† (kg/m^2)	33 ± 10	31 ± 7	0.5
Tobacco use‡	7 (29)	7 (33)	1.0
Fracture type‡§			
B	10 (42)	6 (29)	0.5
C	14 (58)	15 (71)	0.5
Time to surgery† (days)	2 ±2	2± 2	0.9
Open fracture‡	12 (50)	12 (57)	0.8
Complications‡			
Heterotopic ossification	13 (54)	7 (33)	0.2
Grade-III or IV heterotopic ossification	4 (31)	2 (33)	1.0
Return to operating room for heterotopic ossification excision	3 (12)	0	0.2
Manipulation	3 (12)	0	0.2
Postoperative infection	2 (8)	2 (9)	1.0
Nonunion	1 (4)	8 (38)	0.007

*The Fisher exact test or t test, as appropriate. †The values are given as the mean and the standard deviation. ‡The values are given as the number of patients, with the percentage in parentheses. §Type B is a partial articular fracture, and type C is complete articular involvement.

	Nonunion (N = 9)	Union (N = 36)	P Value*
Age† (yr)	44 ± 18	45 ± 15	0.8
Sex‡			
Male	2 (22)	18 (50)	0.3
Female	7 (78)	18 (50)	0.3
Tobacco use‡	4 (44)	10 (28)	0.4
Fracture type‡§			
B	2 (22)	14 (39)	0.5
C	7 (78)	22 (61)	0.5
Time to surgery† (days)	1 ±2	2± 2	0.3
Open fracture‡	3 (33)	21 (58)	0.3
Postoperative infection‡	1 (11)	3 (8)	1.0
Radiation therapy‡	8 (89)	13 (36)	0.007

*The Fisher exact test or t test, as appropriate. †The values are given as the mean and the standard deviation. ‡The values are given as the number of patients, with the percentage in parentheses. §Type B is a partial articular fracture, and type C is complete articular involvement.

With the small numbers studied, no significant difference between the groups was detected with regard to the prevalence or severity of heterotopic ossification or the frequency of surgery to excise heterotopic ossification (Table I). Three of forty-five patients (all in the control group) underwent excision of clinically important (grade III or IV) heterotopic ossification (p = 0.2). There was no difference in postoperative range of motion or MEPS. The mean MEPS was 66 points in the control group and 69 points in the treatment group (p = 0.6). The mean elbow flexion and extension were 113_ and 22_, respectively, in the control group and 116_ and 29_ in the treatment group (p = 0.53 and p = 0.18, respectively). The mean pronation and supination were 69_ and 64_, respectively, in the control group and 71_ and 70_ in the treatment group (p = 0.8 and p = 0.54, respectively).

When the rate of complications was investigated, a significant difference between the groups was detected with regard to the frequency of nonunion (Table I). Of the nine elbows with a nonunion in this series, eight were in the treatment group, resulting in a nonunion rate of 38% (eight of twenty-one elbows). In the control group, the nonunion rate was 4% (one of twenty-four elbows). This difference was highly significant (p = 0.007). The group of patients with a nonunion was then compared with the group of patients with union, to detect any risk factors for nonunion other than radiation therapy. There was no difference with regard to age, sex, tobacco use, fracture classification, open or closed injury, or time to surgery (Table II).

The nonunions occurred in seven fractures (four were in the distal end of the humerus; two, in the olecranon; and one, in the proximal end of the ulna) and in two olecranon osteotomy sites.

Discussion

This randomized controlled trial was terminated early because of concerns that postoperative radiation therapy inhibited bone-healing. This finding was unanticipated as other institutions had reported safe use of this intervention [8,9,13]. Stein et al. used a single radiation dose of 700 cGy to prevent heterotopic ossification after high-energy trauma to the elbow[8]. They reported on eleven patients who sustained fracture-dislocations of the elbow and underwent operative fixation. They reviewed radiographs and clinical function twelve months postoperatively and found ten of eleven patients to be without functional limitations. Three patients developed radiographic evidence of heterotopic ossification anteriorly, and one patient had functional limitations related to the heterotopic ossification. All fractures healed without intervention, and the authors identified no complications related to the radiation therapy. They concluded that radiation therapy may lessen the functional loss from heterotopic ossification without affecting healing at the fracture site. Robinson et al. reported single-fraction radiation for the prevention of heterotopic ossification after elbow surgery in fifty-three patients[9]. This was a heterogeneous group of patients in that some were being treated acutely after trauma and others had already developed heterotopic ossification and were returning to surgery for excision of the ossified soft tissues. The authors found that fifteen of forty-three patients with radiographic follow-up had persistent or new heterotopic ossification. However, they also reported that two patients required additional surgery to treat a nonunion. They concluded that radiation therapy appeared to be safe and associated with maintenance of improved motion. Despite no differences in the radiation protocols, our results were not consistent with these reports as we found the radiation therapy group to have a significantly higher nonunion rate compared with the control group.

The effect of ionizing radiation on osteoblasts was studied in vitro by Dudziak et al., who used 0, 40, 400, and 800 cGy and measured the expression of transforming growth factor-beta 1, vascular endothelial growth factor, and alkaline phosphatase[17]. They found dose-dependent decreases in the growth factors at 400 and 800 cGy and concluded that ionizing radiation induces alterations in cytokine profiles and differentiation of osteoblasts. Konski et al. noted decreased osseous ingrowth with use of a porous-coated rod in a rabbit model following 1000-cGy radiation[18].

Trochanteric nonunion after total hip arthroplasty has been shown to be a potential side effect of radiation therapy[19-22]. In those studies, the trochanteric nonunion rates ranged from 12% to 30% when low-dose radiation therapy was used postoperatively; these rates were significantly higher than nonunion rates in patients who had not had radiation therapy[21]. Shielding of the bone-implant interface has been advocated in total hip arthroplasty to negate the possible side effects of radiation on osteoblast function, and doing so has not diminished the efficacy of radiation therapy[23]. However, no study, to our knowledge, has applied this technique to the elbow. Unlike the hip, where the majority of symptomatic heterotopic ossification occurs in the abductors, the elbow can form heterotopic ossification circumferentially. Hastings and Graham described the sites of clinically important heterotopic ossification around the elbow[24]. They found that posterolateral heterotopic ossification is most common, and it can form an osseous bridge extending from the lateral humeral condyle to the posterolateral olecranon and can fill the olecranon fossa. Ectopic bone can also be seen in the collateral ligaments and can be exuberant in the antecubital fossa area, frequently limiting elbow flexion. Therefore, creating radiation windows to protect the fracture sites from the radiation therapy, while still adequately targeting the sites of heterotopic ossification formation, is challenging. Further research is needed to determine the safety and efficacy of limited-field radiation around the elbow acutely after trauma.

The successful use of radiation therapy after heterotopic ossification excision has been well documented[2,7,25-27]. In those studies, radiation therapy was used in conjunction with excision of heterotopic ossification in contrast to our study, in which radiation was used in a prophylactic manner. Heyd et al. reported on nine patients with heterotopic ossification excision in whom doses of 600 to 1000 cGy were used immediately postoperatively[2]. They found no recurrence of heterotopic ossification and reported good functional outcomes. McAuliffe andWolfson reported on the use of radiation therapy with heterotopic ossification excision in eight patients [28]. At the forty-six month follow-up evaluation, they found no clinical or radiographic evidence of recurrence of heterotopic ossification. Although these case series suggest a benefit of radiation therapy at the time of heterotopic ossification excision, further investigation is needed to clearly define its role in that setting. It does appear, however, that low-dose radiation therapy at the time of heterotopic ossification excision can be accomplished safely.

In the present study, on the basis of the power analysis calculations, seventy-three patients per group were needed to demonstrate a reduction in the rate of heterotopic ossification from 35% to 15%. Also, the number of patients who required surgical treatment for clinically important heterotopic ossification was less than anticipated on the basis of previous reports[5]. This may be due to the exclusion of all patients with a head injury, substantial burns, or neurological injury. Ultimately, three of forty-five patients required heterotopic ossification excision.

Even though all three patients were in the control group, we cannot speculate on the efficacy of radiation therapy on the basis of this sample size as the study was underpowered.

The present study has several limitations. The reduced sample size was necessary because of the significant difference in nonunion rates between the treatment and control groups and the consequent study termination; therefore, the efficacy of radiation therapy in prophylaxis against heterotopic ossification cannot be inferred from this study. Also, numerous surgeons and varying techniques of internal fixation were included in the study. n

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