Prevention of Heterotopic Ossification at the Elbow Following Trauma Using Radiation Therapy

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Abstract
The objective of this study was to determine the efficacy of postoperative single dose radiation therapy of 700 centigray on fracture/dislocations of the elbow in the prevention of heterotopic ossification. Eleven patients were reviewed for this study. Each patient sustained high-energy trauma to the extremity causing a fracture/dislocation of the elbow. After open reduction and internal fixation, a postoperative single dose of 700-centigray radiation therapy was administered to the patients within 72 hours of surgery. Primary outcome measurements were clinical physical examination of range of motion and radiographic analysis of heterotopic bone formation at 12 months follow-up. Three of eleven patients (27%) had radiographic evidence of heterotopic ossification formation. Ten of eleven patients (91%) however, were without functional limitations. All fractures healed without complications. There were no complications from the radiation therapy. A single dose of 700-centigray radiation therapy postoperatively within 72 hours may lessen the functional loss from heterotopic ossification formation without effecting healing at the fracture site.

Heterotopic ossification (HO) is a well recognized complication following total joint replacement surgery, spinal cord injury, traumatic brain injury, thermal or electrical burns, and local high energy trauma. Three percent of patients have been found to have HO about the elbow after local trauma. The resultant ectopic bone can cause pain, limited range of motion, and result in impaired function. Heterotopic bone is characterized by spicules of woven bone arranged in parallel arrays surrounded by fibroblasts that enclose a less calcified osteoid. This is the classic picture of mineralization progressing from the periphery toward the center. The osteogenic precursor cell is likely a mesenchymal pluripotent stem cell with the ability to differentiate into bone.

Risk factors for development of HO include: ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis (DISH), posttraumatic arthritis, bilateral hypertrophic osteoarthritis, previous surgical procedures, extensive trauma occurring during an injury or an operation, and most importantly a previous history of HO formation.

Formation of HO about the hip after fractures or after total hip arthroplasty in high-risk patients is well described, and the prevention with radiation has been documented in the literature.

Brooker devised the widely accepted classification of HO about the hip. Class I includes isolated bone islands on radiographs. Class II has greater than one centimeter of distance between ossifications. Class III has less than one centimeter of distance between ossifications and Class IV is defined as bony ankylosis. Hastings and Graham proposed a classification of upper extremity HO. Class I is defined by radiographic evidence of HO without functional impairment. Class II has radiographic HO with functional impairment and Class III is characterized by ankylosis. It is difficult to decide which patients should undergo radiation therapy. There are a small percentage of high-risk patients who have local elbow injuries and an even smaller number of patients who have HO after local trauma at the elbow.

Prevention of HO includes anti-inflammatory medication, diphosphonate, and radiation therapy. A majority of the literature on prevention of HO concerns posttraumatic or post-arthroplasty hip HO. This literature has been applied to other joints in the past, however; to date, there is no reported

series on the prevention of HO at the elbow using radiation therapy.

**Materials and Methods**

Since 1997, 19 patients who sustained a fracture/dislocation of the elbow were treated at our institution with radiation therapy to prevent the development of heterotopic ossification about the elbow. A total of eight patients were excluded from our study; three who postoperatively developed heterotopic bone and received radiation after excision and five others who received radiation after revision surgery secondary to loss of fixation. The remaining 11 patients were reviewed for this study. There were three males and eight females. The average age was 51 years. All patients sustained a fracture/dislocation of the elbow and had operative treatment within an average of five days of the injury (range: 0 to 16 days). With the exception of one patient who was injured in a motor vehicle accident, all of the patients were injured secondary to a fall. Five patients injured their dominant extremity and six their non-dominant extremity.

Six patients sustained radial head fractures. Five of these were treated with radial head excision with titanium implants. In addition to the radial head excision, five of these patients were treated with multiplanar elbow external fixators. One of these patients additionally had a coronoid fracture and another an olecranon and coronoid fracture. The patient with a radial head fracture not requiring excision and titanium implant sustained concurrent coronoid and olecranon fractures. Three patients sustained intra-articular distal humerus fractures (Table 1).

All patients received a single non-fractionated dose of 700 centigray of radiation at an average of two days following surgery (range: 1 to 3 days). The patients received anterior-posterior/posterior-anterior radiation dosing. Megavoltage radiation was used in all cases. The dose was defined at the midline of the elbow.

All patients began range of motion exercises within one week of surgery either out of their brace or within the multiplanar external fixator. Average follow-up was 12 months (range: 9 to 24 months). Radiographs taken at follow-up office visits and range of motion evaluation were used to evaluate patients for the development of heterotopic bone. Each patient was categorized into the Hastings and Graham upper extremity heterotopic ossification classification.

**Results**

There were no complications from the radiation therapy. The average post-operative flexion/extension arc of motion on latest follow-up was 114.5°. Two patients had arcs of motion less than 100°. Ten of the eleven patients had full pronation and supination upon latest follow-up examination. The average pronation/supination arc of motion was 173°. The average range of motion was 85.9° for pronation and 87.3° for supination.

Two patients experienced decreased sensation postoperatively along the distribution of the ulnar nerve. Both patients continue to have this complaint. One of these patients additionally sustained an injury to the radial nerve that was documented postoperatively. The neuropraxia has resolved upon follow-up examination. Six patients in the study required a second surgery. Five had removal of the external fixators and one a removal of hardware. These patients did not receive repeat radiation treatments after the second surgical procedure.

Anterior-posterior and lateral radiographs of the elbows were reviewed by an independent third party. Three of eleven patients developed heterotopic ossification. All three had ossification noted anterior to the elbow joint within the brachioradialis muscle. Clinically, only one of these patients had restricted range of motion in the flexion/extension arc. Two patients were classified as Hastings and Graham class I, and one patient class II.

**Table 1** Patient Demographics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Injury</th>
<th>Postop ROM Extension/Flexion</th>
<th>Hastings and Graham Supination/Pronation</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>F</td>
<td>Right radial head/coronoid</td>
<td>10°-100°</td>
<td>60°/90°</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>F</td>
<td>Left olecranon</td>
<td>15°-135°</td>
<td>90°/90°</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>M</td>
<td>Left radial head</td>
<td>30°-130°</td>
<td>90°/90°</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>F</td>
<td>Left distal radius, olecranon, coronoid</td>
<td>10°-130°</td>
<td>90°/45°</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>F</td>
<td>Left comminuted distal humerus</td>
<td>30°-120°</td>
<td>90°/90°</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>F</td>
<td>Right olecranon, coronoid radial head</td>
<td>0°-135°</td>
<td>90°/90°</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>M</td>
<td>Left supracondylar humerus</td>
<td>5°-120°</td>
<td>90°/90°</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>51</td>
<td>F</td>
<td>Right distal humerus</td>
<td>0°-120°</td>
<td>90°/90°</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>75</td>
<td>F</td>
<td>Right radial head</td>
<td>30°-130°</td>
<td>90°/90°</td>
<td>0</td>
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<tr>
<td>10</td>
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<tr>
<td>11</td>
<td>54</td>
<td>M</td>
<td>Left radial head</td>
<td>0°-120°</td>
<td>90°/90°</td>
<td>1</td>
</tr>
</tbody>
</table>
Discussion

There is no previously reported series on immediate radiation therapy after operative treatment of elbow fracture/dislocations. Radiation therapy of 700 centigray administered within three days after the open reduction and internal fixation of a fracture/dislocation has the beneficial result of minimizing the effects of HO formation at the elbow. None of the patients in the study needed to have HO excision after the radiation therapy. Ten of the eleven (92%) patients had no functional limitations on physical examination. There were no complications from the radiation therapy. There were no infections or incision site healing complications. All fractures were united at the latest follow-up examination. Only one patient was classified as Hastings and Graham class II. Graham reports that radiation treatment is contraindicated after open reduction and internal fixation because of an increased risk of non-unions. Our results show that all fractures united after a single dose of 700 centigray.

In 1975, Chalmers reported that for bone formation to occur in soft tissues three conditions must be present. These conditions include an inducing agent, an osteogenic precursor cell, and an environment conducive to osteogenesis. In 1980, Michelson found that forcible mobilization of an immobilized rabbit knee caused ossification in the quadriceps muscle. Damaged cells may release inductive factors that elicit a bone forming response from the mesenchymal cell. Urist studied extracts from rabbit bone and discovered the inductive substance triggered migration and differentiation of the mesenchymal cells into cartilage and bone forming cells. This inductive substance is called bone morphogenetic protein (BMP).

Radiation therapy is thought to disrupt the mechanism of heterotopic bone formation in several ways. The radiation is directed toward the pluripotent mesenchymal cell. These cells may be more radiosensitive than the surrounding osteoblasts, therefore sparing the native cells. The mesenchymal cells respond to osteogenic mediators (BMP) produced from local cells including: monocytes, macrophages, and osteocytes. These osteogenic mediators induce the progression from mesenchymal cell to heterotopic bone. Radiation may disable the mesenchymal cell’s ability to respond to the osteogenic mediators. There is a critical point in the pathway of bone formation when the signal from the osteogenic mediators must be received by the pluripotent cell. A delay in radiation therapy may therefore be less efficacious. The radiation therapy may also inactivate the ability of the local cells to release osteogenic mediators that act on the mesenchymal cells. This may explain the fact that mesenchymal cells are not directly affected by the radiation and therefore native osteoblasts spared damage. Prevention of HO after trauma to the elbow is a challenge to the orthopaedic surgeon. Pharmacologic agents have the disadvantage of systemic effects. Nonsteroidal anti-inflammatory agents all have varying degrees of ulcerogenic and nephrotoxic propensity. They may also interfere with fracture healing. Diphosphonates that inhibit mineralization are characterized by poor gastric absorption and gastrooesophageal irritation, and often are poorly tolerated by patients. Radiation therapy is a local treatment that has been adjusted to limited-field, low-dose radiation, and single non-fractionated dosing.

Coventry and Scanlon first described the use of radiation therapy to prevent ectopic bone growth in 1981. They originally used 2000 centigray in a divided dose regimen over 10 days. Since then, the dose has been decreased to a single 700 to 800 centigray dose delivered to a limited field within four days postoperatively. A prospective study confirmed the efficacy of 1000 centigray in the prevention of HO after total hip arthroplasty (THA) in high-risk patients. The dose was given in 200 centigray over five to seven days. Single dose radiation therapy has also been shown to be effective in inhibiting HO after THA using a single dose of 600 centigray. Similarly, a 700 rad non-fractionated dose delivered within 3 postoperative days prevented the development of HO in high-risk patients. In a prospective randomized study of preoperative versus postoperative radiation therapy for prevention of HO about the hip in high-risk patients, a single dose of 700 centigray given four hours preoperatively was shown to be equally efficacious as the standard postoperative protocol. This information can be extrapolated to other joints including the elbow.

McAuliffe and Wolfrom reported eight cases of excision of elbow heterotropic ossification followed by 1000 centigray radiation treatment in five fractions over seven days. This therapy began on the first postoperative day. Excision of the heterotropic bone occurred at an average of seven months after the injury. The mean follow-up was 46 months. There were no complications to the radiation therapy and there were no recurrences of heterotropic bone formation.

The use of radiation therapy does raise the concern of the formation of a radiation-induced sarcoma. This rare complication must be considered when informing patients of using an elective dose of radiation on a benign condition such as elbow trauma. Retrospective studies of patients with radiation-induced sarcomas and patients treated with radiation for ankylosing spondylitis (AS) revealed no induced malignant growths at doses less than 3000 centigray over a three-week period. Kim reported forty-seven cases of radiation-induced sarcomas discovered over a fifty-year period. There were 20 soft-tissue sarcomas and 27 bone sarcomas that had latent periods from irradiation to diagnosis of sarcoma of 11 to 12 years. Radiation doses were between 2700 centigray to 7500 centigray.

A limitation of this study is the one-year follow-up. This may not be an adequate amount of time to define all the possible complications from radiation therapy. Additionally, the small numbers of patients that have elbow fracture/dislocations limit the sample size. The lack of a control group and lack of comparison to other methods of prophylaxis limit the possible conclusions of this study.
Additional studies including clinical prospective randomized controlled projects are needed to truly define the efficacy of radiation therapy to prevent HO at the elbow. Increasing experience with lower dose radiation as well as preoperative dosing has been changing institutional protocols. Longer follow-up with these patients will also enlighten clinicians as to the long-term risks associated with radiation therapy.

References