Incidence and Risk Factors of Heterotopic Ossification Following Major Elbow Trauma

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abstract

Full article available online at Healio.com/Orthopedics. Search: 20120525-18

Heterotopic ossification is a common complication of Orthopaedic Trauma Association (OTA) type C distal humerus fractures and unlnohumeral fracture dislocations. The purpose of this study was to precisely define the incidence of heterotopic ossification following major elbow trauma and to identify risk factors for the development of clinically significant heterotopic ossification and for surgical excision of elbow heterotopic ossification.

Current Procedural Terminology codes identified 156 patients who underwent operative intervention for a distal humerus fracture or an unlnohumeral fracture dislocation at 2 Level I trauma centers over 6 years. The incidence of elbow heterotopic ossification was recorded at >90 days following the definitive procedure. Risk factors for the development of class 3 or 4 heterotopic ossification and for surgical excision of heterotopic ossification were evaluated using separate multivariable logistic regression analyses. Brooker class 3 or 4 heterotopic ossification occurred following 18 (14%) of 125 distal humerus fractures, 15 (22%) of 69 OTA type C distal humerus fractures, and 11 (35%) of 31 unlnohumeral fracture dislocations. Surgical excision of heterotopic ossification was performed after 12 (10%) of 125 distal humerus fractures, 10 (14%) of 69 OTA type C distal humerus fractures, and 8 (26%) of 31 unlnohumeral fracture dislocations. Sustaining a severe elbow injury ($P<.05$) or a delay of fixation ($P=.05$) was found to be independent risk factors for Brooker class 3 or 4 heterotopic ossification. Severe elbow injury ($P<.05$) and male sex ($P<.05$) were associated with operative excision of heterotopic ossification.

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doi: 10.3928/01477447-20120525-18
Heterotopic ossification of the elbow is a posttraumatic complication that typically presents with swelling and loss of range of motion (ROM) within months of the inciting injury.\textsuperscript{1,2} One of the difficulties in studying elbow heterotopic ossification is the lack of a consistently used classification system; \textgreater15 classification systems exist.\textsuperscript{1,3,4} Although created for heterotopic ossification about the hip, the Brooker classification system is the most commonly used classification for elbow heterotopic ossification.\textsuperscript{5} As a consequence of the numerous classification systems, the incidence of heterotopic ossification in the literature ranges from 0\% to 49\% following distal humerus fractures,\textsuperscript{5-9} and from 4\% to 18\% following ununlar fracture dislocations.\textsuperscript{10-12} Unacceptable loss of motion or, less frequently, neurovascular compromise are indications for surgical excision of heterotopic ossification.\textsuperscript{13,14} The reported rate of reoperation for heterotopic ossification following distal humerus fractures ranges from 12\% to 21\% and from 10\% to 15\% following ununlar fracture dislocations.\textsuperscript{11,15,16}

Numerous risk factors, including head injury, duration of intubation, Injury Severity Score (ISS), delay from injury to surgery, burn, spinal cord injury, and number of operations, have been proposed as contributing to the development of heterotopic ossification following trauma, but the literature lacks multiple-variable analyses.\textsuperscript{1,17-24} The importance of these risk factors is to aid in the determination of who would benefit from heterotopic ossification prophylaxis, such as low-dose radiation and nonsteroidal anti-inflammatory drug (NSAID) therapy.\textsuperscript{25-27} The primary objectives of the current study were to precisely define the incidence of clinically significant heterotopic ossification following distal humerus fractures and elbow fracture dislocations and to determine risk factors for Brooker class 3 and 4 heterotopic ossification and for operative excision of heterotopic ossification. The secondary objective was to establish a correlation between Brooker heterotopic ossification and elbow motion. The hypothesis was that elbow fracture dislocations and type C distal humerus fractures would have a high rate of heterotopic ossification and require more secondary surgeries. It was also hypothesized that \textgeq1 variables indicative of a high-energy injury, such as ISS, duration of intubation, delay in fixation, or number of surgeries within the first 90 days, would be independent risk factors for heterotopic ossification.

**Materials and Methods**

Current Procedural Terminology codes identified 634 patients with 635 injuries who underwent operative intervention for a distal humerus fracture or elbow fracture dislocation between January 1, 2002, and December 31, 2007, by 20 surgeons (L.K.C., W.O.) at 2 Level I trauma centers. Institutional Review Board permission was obtained for this study. Inclusion criteria were age 18 years or older at the time of injury, distal humerus fracture (Orthopaedic Trauma Association [OTA] classification 31-A, 31-B, or 31-C) or elbow fracture dislocation (OTA 41-B or 41-C), and \textgeq90 days of follow-up from the definitive surgical procedure. Patients were excluded for the following reasons: inadequate follow-up (n=105), age younger than 18 years (n=228), incorrect diagnosis (n=127), iatrogenic fracture (n=1), amputation as the definitive treatment (n=1), unobtainable follow-up radiographs (n=15), and pathologic fractures (n=2). The remaining 155 patients with 156 injuries were included in this study.

The electronic medical records of these patients were reviewed for patient demographic and injury data, including delay from injury to surgery, total number of surgeries within the first 90 days, ISS, sex, fracture type, final ROM, reoperations for heterotopic ossification, duration of intubation, age, head injury, open injuries, bone grafting, injury mechanism, burn, and spinal cord injury. Injury radiographs were reviewed and classified according to the OTA classification system of distal humerus fractures. According to this system, type A fractures are extra-articular, type B are partial articular, and type C are complete articular fractures.

Closed head injury was determined by a subdural hematoma, epidural hematoma, subarachnoid hemorrhage, cerebral edema, or acute shear injury on computed tomography (CT) scan at the time of admission. Patients who did not warrant a head CT clinically were considered to be without significant closed head injury.

Injury Severity Scores at admission were gathered by reviewing the existing trauma database at both institutions. For a few patients for which this was not available, the ISS was calculated retrospectively by an author (K.D.). No patient received heterotopic ossification prophylaxis.

Postoperative anteroposterior and lateral elbow radiographs taken at least 90 days after the definitive operative procedure but prior to late revision surgery were evaluated using the Brooker classification for heterotopic ossification.\textsuperscript{3} Although originally intended for the classification of heterotopic ossification about the hip, the Brooker classification is the most readily identified classification system for heterotopic ossification, including heterotopic ossification about the elbow. In the Brooker classification system, class 1 heterotopic ossification is islands of bone within the soft tissue, class 2 heterotopic ossification includes bone spurs extending from proximal or distal to the joint but with \textlessthan 1 cm between the opposing surfaces, class 3 heterotopic ossification includes bone spurs with \textlessthan 1 cm between the nearest opposing ends, and class 4 heterotopic ossification is complete radiographic bridging callus across the joint. In addition, proximal radioulnar joint heterotopic ossification was considered to be an all-or-nothing phenomenon, with proximal radioulnar synostosis considered Brooker class 4 heterotopic ossification. Proximal radioulnar synostosis considered Brooker class 4 heterotopic ossification.
joint synostosis was too uncommon to be considered a separate variable; however, it was too important clinically to be excluded from this analysis. Brooker class 3 and 4 heterotopic ossification were considered clinically significant.

Statistical analyses were performed using SAS version 9.1.3 software (SAS Institute, Cary, North Carolina) and R version 2.7.1. (The R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were used to explore all variables and to calculate the incidence of class 3 or 4 heterotopic ossification and the need for surgical excision of elbow heterotopic ossification. Wilcoxon rank sum test for continuous variables and Fisher’s exact test for dichotomous variables were used to examine the univariate association between patient, injury, and clinical risk factors and the outcomes of the incidence of clinically significant heterotopic ossification and operative excision of heterotopic ossification. Wilcoxon rank sum test and Kruskal-Wallis test were performed to evaluate differences in elbow ROM across heterotopic ossification classification groups.

Risk factors that were significant in univariate analysis with a $P<.10$ were entered into multiple-variable logistic regression analyses. The risk factors tested in the univariate analysis were sex, age, high- vs low-energy mechanism, number of operations within the first 90 days, open vs closed injuries, ISS, duration of intubation, head injury, delay from injury to surgery, and severity of injury. All statistical tests were two-tailed, with $P\leq.05$ considered significant.

A secondary multiple-variable analysis was conducted, considering OTA type C fractures as severe and eliminating ulnohumeral fracture dislocations from the analysis to test the significance of distal humerus fracture type separately.

**RESULTS**

Demographic characteristics are presented in Table 1, and injury characteristics are presented in Table 2. Ten percent (16/156) of elbow injuries had a concomitant closed head injury. The average ISS score was 16.8 (range, 9-43). One patient sustained a burn injury, and 1 patient sustained a spinal cord injury. The average duration of intubation for all patients was 1.3 days (range, 0-25 days). Of the 28 of the patients requiring at least 1 day of ventilator support following operative treatment, the average length of intubation was 7.25 days, with a median duration of 4 days. The average delay until definitive fixation was 5.9 days (range, 0-46 days), with a median of 3 days following the injury.

Radiographic follow-up occurred an average of 47 weeks after the definitive operative intervention, with a median follow-up of 32 weeks and 1 day. The incidences of heterotopic ossification and surgical excision of heterotopic ossification following severe elbow injuries are detailed in Table 3. Following OTA type C distal humerus fractures, 22% (15/69) of patients developed clinically significant heterotopic ossification and 14% (10/69)
required surgical excision. Elbow fracture dislocations had a 35% (11/31) incidence of clinically significant heterotopic ossification and a 26% (8/31) reoperation rate for surgical excision of heterotopic ossification. Two patients who required surgical excision of heterotopic ossification following elbow fracture dislocation had proximal radioulnar joint synostosis. The average time from operative fixation to heterotopic ossification excision in those 20 patients was 35.3 weeks (range, 5.1-134 weeks). Nineteen of the 20 patients who underwent surgical excision of heterotopic ossification had class 3 or 4 heterotopic ossification, and 1 patient had class 2 heterotopic ossification.

Univariate analyses for radiographic heterotopic ossification and reoperation for excision of heterotopic ossification are shown in Table 4. Delay of fixation, duration of intubation, number of initial operations, sex, and severe injury displayed significance at P<.10 for both outcomes, while ISS had a P value <.10 for radiographic heterotopic ossification and P=.12 for surgical excision of heterotopic ossification. All 6 of these variables were therefore included in the multiple variable

### Table 3

#### Incidence of Elbow Heterotopic Ossification

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Brooker HO Class, n/N (%)</th>
<th>No. HO Excisions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1-4</td>
</tr>
<tr>
<td>OTA type A distal humerus fracture</td>
<td>23/29 (79)</td>
<td>6/29 (21)</td>
</tr>
<tr>
<td>OTA type B distal humerus fracture</td>
<td>17/27 (63)</td>
<td>10/27 (37)</td>
</tr>
<tr>
<td>OTA type C distal humerus fracture</td>
<td>42/69 (61)</td>
<td>27/69 (39)</td>
</tr>
<tr>
<td>All distal humerus fractures</td>
<td>82/125 (66)</td>
<td>43/125 (34)</td>
</tr>
<tr>
<td>Elbow fracture/dislocation</td>
<td>12/31 (39)</td>
<td>19/31 (61)</td>
</tr>
</tbody>
</table>

**Abbreviations:** HO, heterotopic ossification; OTA, Orthopaedic Trauma Association.

### Table 4

#### Univariate Analysis of Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Brooker HO Class 3 or 4</th>
<th>Reoperation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>.52</td>
<td>.33</td>
</tr>
<tr>
<td>ISS</td>
<td>.08</td>
<td>.13</td>
</tr>
<tr>
<td>Delay from injury to ORIF</td>
<td>.001</td>
<td>.01</td>
</tr>
<tr>
<td>Duration of intubation</td>
<td>.04</td>
<td>.05</td>
</tr>
<tr>
<td>No. of operations</td>
<td>.02</td>
<td>.04</td>
</tr>
<tr>
<td>Head injury</td>
<td>.50</td>
<td>.43</td>
</tr>
<tr>
<td>Sex</td>
<td>.05</td>
<td>.01</td>
</tr>
<tr>
<td>Severe fracture type</td>
<td>.002</td>
<td>.01</td>
</tr>
<tr>
<td>Open vs closed</td>
<td>.28</td>
<td>.40</td>
</tr>
<tr>
<td>High vs low energy</td>
<td>.90</td>
<td>.47</td>
</tr>
</tbody>
</table>

**Abbreviations:** HO, heterotopic ossification; ISS, Injury Severity Score; ORIF, open reduction and internal fixation.
analysis for Brooker heterotopic ossification and reoperation (Tables 5, 6). Severe injury and delay from injury to fixation (P = .05) were independent risk factors for class 3 or 4 radiographic heterotopic ossification. Sex (P < .05) and severe injury (P < .05) were independent risk factors for surgical excision, with delay in fixation (P = .06) approaching significance. The same multiple variable analysis was performed, excluding elbow fracture dislocations, and OTA type C distal humerus fractures were found to be an independent predictor (P < .05) of elbow heterotopic ossification compared with type A and B fractures.

The final ROM in relation to radiographic heterotopic ossification is demonstrated in Table 7. The mean ROM for patients with Brooker class 0 (no radiographic heterotopic bone), 1, or 2 heterotopic ossification was 102°, compared with 48° for patients with Brooker class 3 or 4 heterotopic ossification (P < .0001).

**Discussion**

The current study found that 14% of all distal humerus fractures formed clinically significant heterotopic ossification (Brooker 3 or 4), and 10% required surgical excision. Heterotopic ossification was more common after OTA type C distal humerus fractures, with 20% resulting in class 3 or 4 heterotopic ossification and 14% requiring surgical excision. Kundel et al. reported that 49% of intra-articular distal humerus fractures (OTA type B and C) developed heterotopic ossification and 10% developed Brooker class 4 heterotopic ossification. This difference likely reflects a difference in classification system; however, the current authors believe that the rate of clinically significant heterotopic ossification is the most applicable information to orthopedic surgeons treating these fractures.

The rate of heterotopic ossification after elbow fracture dislocations has been reported to range from 5% to 18%. In the current study, clinically significant heterotopic ossification (Brooker class 3 or 4 or proximal radioulnar joint synostosis) formed after 35% of elbow fracture dislocations, and 26% of these required excision, more than in previously published series. The increased frequency of heterotopic ossification in the current study may be related to the selection bias of high-energy multisystem traumas that present to Level I trauma centers. The study’s results confirmed the hypothesis that heterotopic ossification occurs more frequently after severe elbow injuries. In addition, increased delay from injury to fixation was found to be an independent risk factor for clinically significant heterotopic ossification (P = .05) and approached significance for reoperation (P = .06). Other variables hypothesized to be significant, such as ISS, duration of intubation, and ISS, approached significance for reoperation (P = .05).

**Table 5**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture type</td>
<td>6.31</td>
<td>1.72-23.71</td>
<td>.006</td>
</tr>
<tr>
<td>&gt;1 vs 1 operation</td>
<td>2.02</td>
<td>0.8-5.09</td>
<td>.14</td>
</tr>
<tr>
<td>Delay from injury to ORIF</td>
<td>1.06</td>
<td>1.00-1.13</td>
<td>.05</td>
</tr>
<tr>
<td>Duration of intubation</td>
<td>2.27</td>
<td>0.64-8.11</td>
<td>.20</td>
</tr>
<tr>
<td>Sex</td>
<td>2.1</td>
<td>0.81-5.4</td>
<td>.13</td>
</tr>
<tr>
<td>ISS</td>
<td>0.96</td>
<td>0.74-1.25</td>
<td>.77</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ISS, Injury Severity Score; ORIF, open reduction and internal fixation.

*a*Orthopaedic Trauma Association (OTA) type C fractures and elbow fracture/dislocations vs OTA type A and B fractures.

**Table 6**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture type</td>
<td>5.84</td>
<td>1.2-28.3</td>
<td>.03</td>
</tr>
<tr>
<td>&gt;1 vs 1 operation</td>
<td>1.83</td>
<td>0.62-5.4</td>
<td>.27</td>
</tr>
<tr>
<td>Delay from injury to ORIF</td>
<td>1.07</td>
<td>1.0-1.14</td>
<td>.06</td>
</tr>
<tr>
<td>Duration of intubation</td>
<td>2.68</td>
<td>0.65-10.98</td>
<td>.17</td>
</tr>
<tr>
<td>Sex</td>
<td>3.74</td>
<td>1.11-12.57</td>
<td>.03</td>
</tr>
<tr>
<td>ISS</td>
<td>0.94</td>
<td>0.69-1.27</td>
<td>.67</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval; ISS, Injury Severity Score; ORIF, open reduction and internal fixation.

*a*Orthopaedic Trauma Association (OTA) type C fractures and elbow fracture/dislocations vs OTA type A and B fractures.

**Table 7**

<table>
<thead>
<tr>
<th>Brooker HO Class</th>
<th>Total ROM, deg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>104</td>
</tr>
<tr>
<td>1</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
</tr>
</tbody>
</table>

Abbreviations: deg, degrees; HO, heterotopic ossification; ROM, range of motion.
tubation, and number of initial surgeries, did not reach statistical significance. Including 6 variables in the model resulted in too many variables relative to the number of injuries, but the authors felt this was necessary due to the clinical feasibility of all 6 risk factors.

Male sex ($P<.05$) was an independent risk factor for heterotopic ossification excision but had no statistical correlation with radiographic heterotopic ossification ($P=.13$). Men represented nearly half (76/156) of the patients in this series, with a relatively even distribution among the injury patterns. This suggests that men may be less tolerant of restricted elbow motion and more willing to undergo the risks of operative intervention for resection of elbow heterotopic ossification. In a retrospective review of 20 surgeons, it is impossible to state the exact criteria for excision of heterotopic bone, but the general approach has been to thoroughly discuss the risks of surgical intervention with patients with unacceptable clinical motion loss and let them decide on secondary surgery. Future prospective research will be needed to further address the influence of sex, as well as other factors, such as occupation, on patient tolerance for lost elbow motion.

Head injury is one of the most commonly referenced risk factors for heterotopic ossification.17,28,29 Garland and O’Hollaren17 reported that 16 of 18 patients with fractures or dislocations about the elbow who were admitted to the adult head trauma service at 1 hospital over 9 years in the 1970s developed heterotopic bone formation about the elbow. They did not define the neurologic criteria for head injury, but 8 of the 18 patients in their study had what they described as spastic quadriparesis, which is likely indicative of a severe head injury. Computed tomography scans were invented during this time period but were not yet widely used clinically, so it is feasible that these clinically diagnosed head injuries were more severe than many of the radiographically diagnosed head injuries in the current study. Perkins and Skirving29 performed a case-control series examining the volume of callus formation in adults with femur fractures and found it to be significantly increased in adults with head injury. In a retrospective review, Pape et al21 reported that the incidence of heterotopic ossification in severely traumatized patients without head injuries was essentially the same as those with head injuries. They surmised that other etiologic factors predisposed patients to form heterotopic ossification, in particular duration of intubation.21

Head injury did not correlate with the development of class 3 or 4 heterotopic ossification ($P=.50$ and $P=.43$, respectively) or with heterotopic ossification resection ($P=.43$) in the current univariate analysis. However, similar to Pape et al,21 the current study used a broader definition of closed head injuries than that used by Garland and O’Hollaren17 or Perkins and Skirving.29 It is likely that head injury must be stratified by severity when assessing its contribution to the formation of heterotopic bone, as previously suggested by Lal et al.24 A patient with a head injury causing spasticity or other neurologic compromise is a different clinical entity than a patient with a small subdural hematoma without neurologic impairment. Unlike the findings of Pape et al,21 duration of intubation was not found to be a clinically significant predictor of Brooker heterotopic ossification or reoperation in the current multiple variable regression analysis ($P=.20$ and $P=.17$, respectively).

Kundel et al8 and Ilahi et al20 reported that a delay of 24 to 48 hours from injury to definitive fixation led to an increase in heterotopic ossification following elbow trauma. Of 41 elbow injuries reviewed by IIahi et al,20 no fractures fixed within the first 48 hours developed grade 2 through 4 heterotopic ossification, compared with 33% of patients treated after 48 hours. However, neither Ilahi et al20 nor Kundel et al8 performed a multiple-variable regression analysis to assess the contribution of other risk factors.

The average delay in fixation in the current study was 5.9 days (median, 3 days; range, 0-46 days). Statistically, this was considered a continuous variable, so the authors cannot recommend a given time period in which fixation should occur. Reasons for delaying surgery vary significantly, from comorbid conditions in multisystem traumas to soft tissue injuries requiring delayed definitive fixation to surgeon and operating room availability in the ambulatory setting. Theoretically, the delay in fixation could allow further differentiation of pluripotent stem cells, which then results in bone formation in undesired locations following delayed fixation.

Casavant and Hastings30 reported that multiple operations may be a risk factor for elbow heterotopic ossification, but it was not statistically significant in the current study ($P=.14$). Patients who require multiple initial surgeries typically have large open wounds, compromised soft tissue envelopes, infection, or neurovascular injuries, which put them at increased risk of nonunion, infection, and wound-healing complications.31,33 Consequently, this patient population is inherently risky to treat with heterotopic ossification prophylaxis and requires surgery regardless of the risk of secondary heterotopic ossification formation. Thus, whether these patients are at an increased risk of heterotopic ossification probably would not change the clinical decision making regarding heterotopic ossification prophylaxis.

Although the Injury Severity Score system has flaws, it is a well-known injury grading system used to quantify systemic injury in multitrauma patients. The Injury Severity Score has been associated with knee ankylosis from heterotopic ossification in 1 study,18 but to the current authors’ knowledge, no large series has examined the relationship of ISS and elbow heterotopic ossification. In the current series, ISS was not found to be predictive of Brooker 3 or 4 heterotopic ossification ($P=.77$) or reoperation ($P=.67$). The lack
of significance of ISS, duration of intubation, mechanism of energy, head injury, and open fractures demonstrate that complex high-energy traumas themselves may not predispose people to form heterotopic ossification, although their sequel type C fractures or delayed fixation could increase a patient’s risk. Other previously described risk factors, such as burns or spinal cord injuries, were unable to be assessed due to their infrequency.

The current study’s secondary hypothesis is that elbow ROM would correlate with Brooker heterotopic ossification was confirmed. Although this seems intuitive, to the authors’ knowledge it has not been clearly delineated in the literature.

The current study’s data supports fracture type and delay of fixation as the most important risk factors for heterotopic ossification after elbow trauma. The surgeon treating distal humerus fractures and elbow fracture dislocations must closely evaluate the need for NSAIDs or radiation prophylaxis, because prophylaxis is not without significant risk. Prolonged disability from elbow stiffness can have a serious functional, economic, and psychosocial impact on a patient’s life. Although heterotopic ossification can be excised surgically with relatively good results, surgical excision is not without risks. Neither institution at which this study was conducted has routinely used heterotopic ossification prophylaxis for this subset of patients.

This study had some limitations, including those present in any retrospective analysis. A larger sample size would have allowed a more precise investigation into the contribution of individual risk factors. Distal humerus fractures and elbow fracture dislocations represent some of the most severe injuries about the elbow, but inclusion of radial head, olecranon, and other fractures about the elbow may have made the risk factor analysis more complete. The absence of a consistently used classification of elbow heterotopic ossification is another drawback to this or any study examining elbow heterotopic ossification. It is also impossible to accurately assess the proximity and 3-dimensional relationship of heterotopic bone using only orthogonal radiographs of the elbow. However, the presence and extent of heterotopic bone on radiographs, even if not anatomically precise, is indicative of a process capable of causing motion loss.

CONCLUSION

The risk of heterotopic ossification and other complications is real when treating patients with distal humerus fractures and elbow dislocations. The results of this study encourage the expedient fixation of these injuries when possible and consideration for heterotopic ossification prophylaxis, particularly in elbow fracture dislocations.

REFERENCES


