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## Prophylaxis against heterotopic ossification after elbow and acetabular fractures — Do we really need it

Rizwan Haroon Rashid,<sup>1</sup> Irfan Qadir,<sup>2</sup> Waseem Ahmed,<sup>3</sup> Masood Umer<sup>4</sup>

### Abstract

**Objective:** To compare the efficacy and safety of prophylactic modalities for heterotopic ossification prevention after elbow and acetabular surgeries.

**Methods:** The retrospective chart review was conducted at the Aga Khan University Hospital and comprised record of patients who underwent open reduction and internal fixation for elbow and acetabular fractures between 2010 and 2013. Data was classified into three groups: Group A patients had received single dose of radiotherapy; Group B patients had received indomethacin, and Group C patients had not received any prophylaxis. Outcome variables included time-to-fracture healing, heterotopic ossification, non-union and wound infection.

**Results:** Of the 104 patients 70 (67.3%) had elbow fractures and 34 (32.7%) had acetabular fractures. Out of the 70 patients with elbow fractures, 28 (27%) were in Group A, 24 (23%) in Group B, and 18 (17%) in Group C. In Group A, 4 (22%) patients had wound infection compared to 1 (5.5%) patient in Group C ( $p=0.131$ ). One (4%) patient in Group B and 1 (5.5%) in Group C developed heterotopic ossification ( $p=0.486$ ). Non-union occurred in 1 (4%) patient in Group B and 1 (5.5%) in Group C. Out of the 34 patients with acetabular fractures, 11 (32.3%) were in Group A, 10 (29.4%) in Group B, and 13 (38.2%) in Group C. In Group A, 2 (18.2%) patients developed wound infection. Only 1 (7.6%) patient in Group C developed heterotopic ossification.

**Conclusion:** No role of radiotherapy or indomethacin was detected in the prevention of heterotopic ossification.

**Keywords:** Heterotopic ossification, Elbow, Acetabulum, Fracture, Pakistan. (JPMA 65: S-87 (Suppl. 3); 2015)

### Introduction

Heterotopic ossification (HO) is a benign process by which trabecular bone forms outside of the skeletal structure, occupying space in soft tissue where it does not normally exist. HO has been recognised to occur in three distinct contexts: trauma, neurological injury and genetic abnormalities. Traumatic HO typically follows fractures, dislocations, operative procedures, and severe burns, most commonly seen around the hip followed by elbow and shoulder joints after fracture and open reduction-internal fixation (ORIF) procedures or arthroplasties.<sup>1,2</sup> The pathogenesis of HO is unclear, but may involve inappropriate differentiation of pluripotent mesenchymal cells into bone-forming cells under the influence of inductive stimuli in a permissive environment.<sup>1-3</sup>

The incidence of HO around elbow joint is estimated to be 3% after local trauma or dislocation<sup>4</sup> and increases up to 15-50% when dislocation is combined with fracture, and to >50% in fractures involving the radial head.<sup>4</sup> The incidence of HO in patients undergoing

acetabular fracture fixation varies depending upon what approach is used, associated injuries, open fracture and can be as high 90%.<sup>2,5-7</sup> Unfortunately, HO is detectable on radiographs as late as 4-12 weeks after injury when no efficient therapy is available. Almost 30% of all patients presenting with HO will develop symptoms, including pain and restricted motion that may require secondary surgical procedures.<sup>8</sup> Surgical excision is the treatment of choice for pre-existing HO, but recurrence rates can be as high as 80-100%. Therefore, prophylaxis with radiotherapy (RT) or non-steroidal anti-inflammatory drugs (NSAIDs) is the mainstay of treatment. The effectiveness of both prophylactic therapies has been extensively studied, but no conclusive data exists to indicate superiority of one treatment modality over the other.<sup>1-3,9</sup>

The current study was planned to review experience of using RT and NSAIDs in the prevention of HO after ORIF for fractures around hip and elbow joints.

### Patients and Methods

The retrospective chart review was conducted at the Aga Khan University Hospital and comprised record of patients who underwent ORIF for elbow and acetabular fractures between 2009 and 2013. Data was classified into three groups: Group A patients had received single

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dose of RT within 24 hours of fracture fixation at a dose of 7Gy; Group B patients had received indomethacin 25mg 3 times a day for 3 weeks, and Group C patients had not received any prophylaxis. The decision of prophylactic modality was based on surgeon's preference. Outcome variables included time-to-fracture healing, HO in terms of radiological and functional failure rates, non-union and wound infection.

The presence of HO was diagnosed both clinically by assessment of the range of movement and radiologically by X-rays. Radiographs were taken at 1.5, 3, 6 and 12 months post-operatively. These films were reviewed by two independent radiologists who were blinded to the method of treatment. In patients with elbow and acetabular fractures, the extent of HO was assessed with and Graham classification<sup>10</sup> and Brooker grading system<sup>11</sup> respectively. All the patients had a minimum of 12-month follow-up, ranging from 13 to 25 months.

SPSS 20 was used for data analysis. Chi square was used for categorical variables and t test for continuous variables.  $P < 0.05$  was considered statistically significant.

## Results

Of the 104 patients, 70 (67.3%) had elbow fractures and 34 (32.7%) had acetabular fractures. Overall mean age was  $44.62 \pm 17.31$  years. All the fractures were close (100%) and the three groups did not differ statistically in terms of age, gender and injury-to-operation time ( $p > 0.05$  each) between the groups.

Out of the 70 patients with elbow fractures, 28 (27%)

were in Group A, 24 (23%) in Group B, and 18 (17%) in Group C. In Group A, 4 (22%) patients had wound infection compared to 1 (5.5%) patient in Group C ( $p = 0.131$ ). One (4%) patient in Group B and 1 (5.5%) in Group C developed HO ( $p = 0.486$ ) (Table-1). The lone Group C patient developed grade III HO with significant functional limitation requiring surgical management. Non-union occurred in 1 (4%) patient in Group B and 1 (5.5%) in Group C.

Out of the 34 patients with acetabular fractures, 11 (32.3%) were in Group A, 10 (29.4%) in Group B, and 13 (38.2%) in Group C. In Group A, 2 (18.2%) patients developed wound infection. Only 1 (7.6%) patient in Group C developed HO requiring surgical excision (Table-2).

Two (6%) patients had non-union at fracture site and underwent revision surgery with bone grafting.

Mean time to fracture healing was comparable among the groups ( $p > 0.05$ ).

The full treatment protocol was not completed in 3 (9%) Group B patients due to noncompliance, and 1 (33%) of them developed HO. Group B patients encountered gastrointestinal disturbances but not significant enough to warrant discontinuation of treatment.

## Discussion

The study failed to demonstrate the role of RT or NSAIDs in the prevention of HO after ORIF for elbow and acetabular fractures. However, these modalities continue to be used widely for HO prevention. The effectiveness of RT is attributed to the radio-sensitivity

**Table-1:** Outcomes in patients with elbow fractures.

Groups	No. of patients	HO	Wound infection	Non-union	Time to fracture healing (months)
A	28	0	4	0	3.5
B	24	1	0	1	4.5
C	18	1	1	1	4
p-value		0.486	0.131	0.486	0.263

HO: Heterotopic ossification.

**Table-2:** Outcomes in patients with hip fractures.

Groups	No. of patients	HO	Wound infection	Non-union	Time to fracture healing (months)
A	11	0	4	0	4
B	10	0	0	0	4.5
C	13	1	1	0	4
P-value		0.435	0.29		0.565

HO: Heterotopic ossification.

of the osteoprogenitor cells present in the early phase of HO development.<sup>2,3</sup> Indomethacin works by inhibiting prostaglandin (PG)-mediated (specifically PGE-2) bone remodelling and also by directly inhibiting the differentiation of osteoprogenitor cells.<sup>3,12,13</sup>

A meta-analysis<sup>1</sup> of seven randomised studies (1,143 patients) comparing RT with NSAIDs for HO prophylaxis in patients undergoing ORIF for acetabular fracture or total hip arthroplasty (THA) demonstrated RT to be more effective than NSAIDs in preventing clinically significant (Brooker Grade 3 or 4) HO (risk ratio = 0.42; 95% CI = 0.18-0.97). The timing of administration is important since the success rate decreases from 98% to 33% after the fourth post-operative day.<sup>14</sup>

The effectiveness of indomethacin in HO prevention was compared with that of radiation in a prospective, randomised trial.<sup>13</sup> which concluded that there is no difference in the rates of HO according to prevention modality. It also noted a significant increase in long bone non-union in patients receiving indomethacin compared to RT (26% vs. 7%; p=0.004). In a study,<sup>15</sup> 142 patients were followed for formation of HO following THA. Of the 11 that underwent a revision procedure secondary to aseptic loosening, 10 belonged to the indomethacin group. Moreover, prolonged use of NSAIDs is associated with gastrointestinal side effects, such as gastritis and ulcer formation. Finally, there are issues of patient compliance with prolonged duration of treatment.<sup>2,15</sup>

However, the use of RT is not free of drawbacks. Potential risks of RT include malignancy, impaired healing, infertility, genetic alteration and there is the issue of availability of RT and its higher cost compared to indomethacin.<sup>2,3</sup> In a review of their 50-year experience of radiation-induced sarcomas, Kim et al<sup>16</sup> reported no cases of bone or soft-tissue sarcomas in patients exposed to doses lower than 30Gy. A randomised controlled trial<sup>9</sup> found no significant differences between the RT and control groups with regard to the prevalence of HO, and post-operative range of motion (ROM). However, the non-union rate in the RT group was exceptionally high 38% which led to early termination of the study.

Since the development and use of NSAIDs and RT for HO prophylaxis, there have been several studies attempting to pinpoint new aspects of HO aetiology and thus direct the development of new prophylactic modalities with increased efficacy and fewer side effects.<sup>4,12</sup> Local use of Noggin,<sup>12</sup> pulsed electromagnetic fields (PEMF) and free radical

scavengers such as allopurinol and N-acetyl cysteine<sup>12</sup> have shown promising results in preventing ectopic bone formation.

The debate continues as to which modality is the best one for the prevention of HO. However, the issues are different from a developing nation's perspective where the debate still moves around the most cost-effective method of treatment. In a healthcare system with inequitable distribution of medical facilities where patients themselves are primary payers of medicare services, radiotherapy is an expensive option. Therefore, treatment of this benign and preventable condition has also become challenging.

In terms of limitations, the retrospective nature and small sample size of the study, its findings cannot be generalised regarding the rationale for choosing prophylaxis modality in individual cases.

## Conclusion

There was no role of RT or NSAIDs in the prevention of HO. Decision should be based on patient's comorbidities, cost, availability of RT, and anticipated compliance with the treatment plan.

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