

Use of Indomethacin for Reducing the Incidence of Heterotopic Ossification after Acetabular Fracture

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Abstract

Background:-Heterotopic ossification (HO) is a common problem with acetabular fracture, usually associated with pain and can severely limit motion in the nearby joint.

Aims:- To evaluate the effect of indomethacin in comparison to placebo in reducing the incidence and severity of heterotopic ossification after acetabular fracture

Patients and methods : - Convenient sample of eighty-three patients that underwent surgery for fixation of acetabular fracture from Oct.2010 to Jun.2013 at Alwasti Teaching Hospital were included in this study. The patients randomized to two groups. The first group consist of 21 patients received 75 mg of indomethacin for six weeks post operatively and the second group of 22 patients received placebo medication (B6 tablet). The patients assessed clinically and radiographically at 3 months of surgery for HO according to Brooker classification, range of motion and rate of mal or non-union. Chi-square test and independent student T test used to confirm significance. $p \leq 0.05$ considered significant.

Results:-The mean age of patients in group (indomethacin group) was 37.2 ± 3.4 SD and of group (placebo group) was 38.1 ± 5.4 SD. The male patients represented 47.8% of indomethacin group and 52.2% of placebo group .No significant difference was reported for mean age, weight or sex distribution ($p=0.3, 0.8$) respectively .The incidence of HO with all grades were higher with placebo group; 68.2% (15 patients out of 22, in comparison to indomethacin group; 33.3 % (7 out of 21) %) but the difference was statistically non-significant. The incidence of >20% reduction in range of motion also non-significantly higher with placebo group in comparison to indomethacin group (66.7, 33.3%) respectively.

Conclusion:-The study showed that indomethacin reduces the incidence and severity of HO in acetabular fracture surgery

Key words; Heterotopic ossification, acetabular fracture, indomethacin

Introduction:-

Heterotopic ossification (HO) is process of trabecular bone formation in non-osseous tissue such as muscle, ligaments and tendon ⁽¹⁾. The main etiological factors behind the development of HO are; traumatic, neurological and genetic factors ⁽²⁾. The open-reduction internal-fixation (ORIF) technique for acetabular fracture represented the most common site for the formation of HO followed by total hip arthroplasty (THA) ^(3, 4).

It is one of the most common complications after acetabular fractures and reconstructive surgery, typically manifests as decreased range of motion at a nearby joint ⁽⁵⁾. The reported incidence of HO with surgically treated acetabular fracture ranged from 18.1-74.3 % ⁽⁶⁾ while the incidence of HO in conservatively treated fractures is only 5 % ⁽⁷⁾. The exact pathophysiology of HO remains unknown. Many factors have been suggested as contributory factors to formation of HO such as prostaglandin activity, specifically PGE-2, hypercalcemia, tissue hypoxia, imbalances between parathyroid hormone activity and calcitonin and prolonged immobilization ⁽⁸⁾. These factors participate in improper differentiation of pluripotent mesenchymal stem cells into osteoblastic precursors ⁽²⁾.

Della Vale ⁽⁹⁾ modified the Brooker classification to three grades based upon AP view of pelvis. Grade A, absence of HO (may be ≥ 1 island of bone of <1 cm in length) .Grade B, presence of ≥ 1 islands of bone of at least 1 cm in length and bone spurs from the pelvis or femur ,1

cm distance between opposing surfaces of bone. Grade C, bone spurs arising from the pelvis or femur with <1 cm between opposing surfaces or apparent bone ankyloses.

Non-steroidal anti-inflammatory drugs (NSAIDs) thought to prevent heterotopic bone formation by inhibiting the early stage of bone formation. Antiinflammatory decreases the inflammatory response by inhibition the prostaglandin H synthase. NSAIDs are also believed to hinder differentiation and migration of precursor cells ⁽¹⁰⁾. The prophylactic type and duration of treatment that recommended for prevention of HO post-surgery for acetabular fracture vary in many centers, but the common prophylaxis is indomethacin in a 25-mg dose, three times daily (or slow release 75 mg once daily), for 7–14 days postoperatively, commenced within 24–48 h after the surgical procedure. While other non-steroidal anti-inflammatory drugs other than indomethacin found to be effective for the prevention of HO following total hip replacements, indomethacin remains the only drug with evidence in preventing HO following acetabular surgery ⁽¹¹⁾

Side effects such as gastric ulcers, renal toxicity and fracture non-union from prophylactic use of NSAIDs with acetabular fracture fixation ascertained ⁽¹²⁾.

Patients and methods : -

A double-blinded randomized control trial conducted in Alwasti Teaching Hospital between Oct.2010-Jun.2013. A convenient sample of 43 skeletally mature adult patients with acute acetabular fracture because of falling from height

and presented with fractures of posterior wall type who operated on by open reduction and internal fixation by posterior approach were included in this study. Chronic user of NSADI before surgery, with burn, and those with associated injury excluded.

After patients consent taken to participate in this study, patients randomized to two groups'. The seniors researchers asked assistants of postgraduate students to prescribe medications and not informed them or the patients about given medication. The patient that operated on in odd day given 75 mg of indomethacin and that who operated on in even day given placebo medication by assistants as we informed later on.

The first group of 21 patients (11 men, 10 women) given 75 mg of indomethacin and antacid to counter a side effect of indomethacin for six weeks starting from the first day post-surgery. The second group of 22 patients (12 men, 10 women) The results revealed that the incidence of HO with all grades was higher with placebo group (15, 68.2%) in comparison to indomethacin group (7, 33.3%) The results demonstrated that the incidence of >20% reduction in range of motion was higher with placebo group (66.7%, 15 cases) in compare to No significant difference was reported concerning incidence of HO grades or incidence of >20% reduction in range of motion between groups of

study when analyzed on gender base. The patients in two groups operated on within 3-5 days of an accident. Non-union status not reported with our cases. indomethacin group (33.3%, 7 cases) but

the difference was statistically non-significant ($p=0.4$) as seen in table.3.

but the difference did not reach the significant level ($p=0.2$) as shown in table.2.

was received placebo medication that had no anti-inflammatory effect (B 6 tablet).

Based upon radiographically A-P view of the pelvis with both hips, Brooker et al ⁽¹³⁾ classified the heterotopic ossification around hip into four types. Class I, the islands of bone within the soft tissues about the hip. Class bone spurs arise from the pelvis or proximal end of the femur leaving about 1 cm between opposing surfaces of the bone. Class III, the spurs of the bone originating from proximal end of the femur or pelvis and reducing the space between opposing bone surfaces to less than one cm. Class IV; bone ankylosing the hip joint. In our study, the radiologist not informed about used medications. CT scanning was did for the patients' pre and post operatively. Statistical analysis: Chi-square test and independent student T test used to confirm significance. $p \leq 0.05$ considered significant.

Results:-

The results showed that the mean age of indomethacin group was $37.2 \pm 3.4SD$ while of placebo group was $38.1 \pm 5.4SD$; mean weight was $72 \pm 3.2SD$ for group I and $71 \pm 4.2SD$ for group II. The male represented 47.8% of first group and 52.2% of later group. No reported significant difference for mean age, weight or sex distribution ($p=0.3, 0.1, 0.8$) respectively as shown in table.1

Table.1.sociodemographic characteristics of studied group

		indomethacin group	placebo group	p-value
		No(SD)	No(SD)	
Age/year		37.2±3.4SD	38.1±5.4SD	0.3
Weight		72±3.2SD	71±4.2SD	0.1
		No (%)	No (%)	
Gender	male	11(47.8%)	12(52.2%)	0.8
	female	10(50%)	10(50%)	

Table.2;-incidence rate of HO grades according to studied groups

broker grades	Groups				p-value
	Indomethacin group(n=21)		Placebo group(n=22)		
Grade 0(no ossification)	14	66.7%	7	31.8%	0.2
Grade I	2	9.5%	4	18.3%	
Grade II	2	9.5%	3	13.6%	
Grade III	2	9.5%	5	22.7%	
Grade IV	1	4.8%	3	13.6%	

Table.3.incidence rate of >20% reduction status of studied groups

>20% reduction	Groups				p-value
	Indomethacin group		Placebo group		
	No.	%	No.	%	
Yes	2	33.3%	4	66.7%	0.4
No	19	51.4%	18	48.6%	

Discussion:-

The ideal prophylactic measure for HO should show a significant reduction in the incidence of formation of trabecular bone, easily used and with a minimal risk of side effects as the patient compliance could affect the success of any drug treatment regimen⁽¹⁴⁾.

Our data indicated that the incidence of HO with all grades in indomethacin group was lower than placebo group but the difference did not reach the significant level as it reported in 7 (33.3%) patients of first group and in 15(68.2%) patients of later group. This finding are in line with Karunakar M A et al⁽¹⁵⁾ who also reported higher incidence but non-significant HO with placebo group in comparison to indomethacin group (59.7% vs. 45.8%). A study conducted by Sagi HC et al⁽¹⁶⁾ not found a notable effect for indomethacin on incidence of HO after acetabular fracture surgery in comparison to placebo group. The same authors was found that 6 weeks of daily 75mg of indomethacin significantly increases the incidence of nonunion compared to placebo while 1 week of 75 mg of indomethacin may reduce the incidence of HO in comparison to placebo without increasing the rate of nonunion ,in addition they found 63% of their patients had poor compliance with indomethacin. Our finding the rate of union with indomethacin in line with the results of a study that conducted by GM Siboto FC⁽¹⁷⁾ who also not reported nonunion status with their cases following indomethacin prophylaxis.

A study was conducted by Moed BR et al⁽¹⁸⁾ concluded that indomethacin prophylaxis was not effective in eliminating heterotopic ossification but the sever HO (Grade III and IV) was significantly reduced. The authors Griffin S M⁽¹⁹⁾ also found no major differences between indomethacin and placebo groups with regard to incidence of moderate and severe HO post-surgery for acetabular fracture.

Randomized trial was conducted by Schafer S J et al⁽²⁰⁾ to compare the effect of indomethacin with different duration of use ,effect of radiation in compare to placebo and found that out of 38 patients who were received complete course ;4 patients was developed HO of Grade III,2 cases was developed HO of Grade III . In group of patients who received incomplete course(less than 6 weeks);2 out of 7 patients was developed HO of Grade IV but no Grade III was reported .2 out of 5

patients of placebo group was developed HO of Grade III and 1of Grade IV.

The Matta J M⁽²¹⁾ in a double-blind randomized study of 57 patients with acetabular fractures did not found significant benefit with indomethacin.

In our study, the incidence of >20% reduction in range of motion was higher in placebo group (66.7%) in compare to 33.3% of indomethacin group in addition most of the cases with 20% reduction in ROM was of patients who had HO of Grade III or IV and this reflect the association between severity of HO and reduction in ROM.

To present time, no prophylactic measure other than indomethacin and radiation used for the inhibition of development of HO but there is conflicting opinions about their effectiveness, even some studies demonstrated them to be useless. For this purposes many researchers shifted to the identification and control of associated risk factors if possible in order to inhibit the generation of HO after acetabular fractures⁽¹⁹⁾.

The Griffin et al⁽¹⁹⁾ and Davis et al⁽²²⁾ concluded that careful surgical technique, debridement of necrotic gluteus minimus and digastric slide osteotomy might reduce HO rates

The results of this study might limited by the fact that the patients discharged from the hospital, they may not take the prescribed medication regularly, and we did not confirmed the drug level by laboratory confirmation .Assigning controls to 'not receiving indomethacin' considered unethical in the light of evidence suggesting the benefit of its administration.

Conclusion:

-indomethacin in 75 mg for six weeks post-surgery for fixation of acetabular fracture insignificantly reduces the risk of heterotopic ossification but not increasing the risk of nonunion.

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