Clinical Article

Indomethacin and heterotopic ossification in acetabular fractures:

A prospective cohort study of the effect indomethacin has on the incidence and severity of heterotopic ossification

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Abstract

Heterotopic ossification (HO) that complicates acetabular fractures is initiated at the time of injury.[19] We hypothesised that indomethacin medication commenced prior to surgery and within the first week following injury would be more effective than post-operative use alone. Over a four-year period 184 consecutive patients with significantly displaced acetabular fractures scheduled for acetabular reconstructive surgery were included in the study.

Fifty-seven patients received indomethacin post-operatively only (Group 1), 95 pre- and post-operatively (Group 2), and 19 received no treatment for various reasons including intolerance of NSAIDs(Group 3). Three patients died and ten were lost to follow-up.

Standard AP radiographs were reviewed at 2 weeks, 6 weeks, 3 months, 6 months and 12 months post-op and were grading as per Brooker on the 3-month follow-up radiograph.

The mean Brooker values for Group 1 = 0.70; Group 2 = 0.33; Group 3 = 1.57. A statistical analysis of the p-values for Group 1 compared to Group 2 = 0.04; Group 1 to Group 3 = 0.002; Group 2 to Group 3 = 0.000006.

Associated injury was the only parameter that correlated with increasing heterotopic ossification, while age, sex, approach and fracture type had no influence.

This study confirms that indomethacin reduces the incidence and severity of HO in acetabular fracture surgery and is more effective if started pre-operatively.

Introduction

Heterotopic ossification (HO) after acetabular fracture and reconstructive surgery has been quoted as being the commonest complication, and has been reported as occurring in 18-90% of cases[2,6,13,14,17,19] with 7-14% being clinically significant.[2,5,6,9,11,14,15,17] The incidence of HO in conservatively treated fractures is only 5%.[19]

Many studies, where indomethacin was administered post-operatively, have demonstrated effective prophylaxis in reducing the incidence of HO.[6,13-16,25] A study by Matta *et al,* the only double blind randomised trial, showed no benefit.[12]

After reviewing the pathophysiology[1,4,21,25] we postulated that the initiating event for the formation of HO was the original trauma and that the surgery potentiates the process of heterotopic bone formation[21] and hence that additional benefit may be achieved if the administration of indomethacin was started prior to surgery.

It was believed that indomethacin would have a better chance of suppressing the HO cascade and thereby decrease the incidence and severity of HO.

This belief made the senior author (GS) change the policy of only giving indomethacin post-operatively to giving it pre-operatively as well.

This change took place only after the first 67 patients had been treated with indomethacin started post-operatively.

The purpose of this study was to retrospectively review the incidence and severity of HO in patients treated surgically for displaced acetabular fractures and to assess the influence of indomethacin commenced pre-operatively, post-operatively or not given at all.

Materials and methods

All patients with displaced acetabular fractures scheduled for reconstructive surgery, and who had no contraindication to surgery, were considered eligible for this study. One-hundred-and-eighty-four patients with acetabular fractures operated on from August 1994 to December 1999 by one surgeon were entered into the study and their clinical records and radiographs were reviewed.

Patients were divided into three groups. Group 1 received indomethacin 25 mg tds, commenced 24 hours post-operatively and continued for a period of 6 weeks. Group 2 received the same dose of indomethacin on admission, and therefore, prior to surgery, and continued for a period of 6 weeks. Group 3 received no indomethacin.

They were followed up at 6 weeks, 3 months, 6 months and 12 months. AP radiographs were taken at each visit and if there was more than 20% restricted range of motion compared to the opposite side this was documented.

Overall 13 patients were excluded: Ten patients were excluded because they were lost to follow-up, and a further three patients died during the follow-up period, leaving 171 patients for review.

From August 1994 until Aug 1996, 57 patients received post-operative indomethacin only, comprising Group 1. Thereafter 95 patients received pre- and post-operative indomethacin, comprising Group 2.

Nineteen patients in whom indomethacin was contraindicated because of previous ulcer or gastrointestinal symptoms, jaundice, haemodynamic instability (in Intensive Care Unit) or clotting abnormality were included in Group 3.

Patient parameters such as sex, age, mechanism of injury, associated injuries, fracture type, number of days from time of injury to surgery, intra-operative blood loss and surgical approach were documented. The mechanism of injury was divided into (1) motor vehicle accident (MVA) passenger; (2) MVA pedestrian; (3) MVA driver; and (4) other *(Figure 1)*. The fractures were grouped into (1) posterior wall; (2) posterior column; (3) transverse; (4) both columns; and (5) 'T' fractures *(Figure 2)*. The associated injuries were divided up into six groups: isolated acetabular fracture, abdominal, chest, head, skeletal injuries and polytrauma. The surgical approaches utilised were (1) Kocher-Langenbeck; (2) ilioinguinal; and (3) combined approach *(Figure 3)*.

Patients were followed up for a minimum of three months. At this visit the Brooker class[3] was documented on an antero-posterior pelvic radiograph by two surgeons. If the Brooker class was 3 or 4, the presence or absence of a restricted range of motion of 20% or more was noted. Fracture union was assessed radiologically.

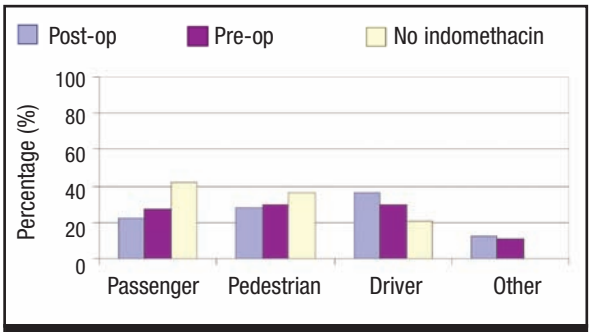

Figure 1: The use of indomethacin in the different modes of injury. It is interesting to note the prevalence of motor vehicle related injury

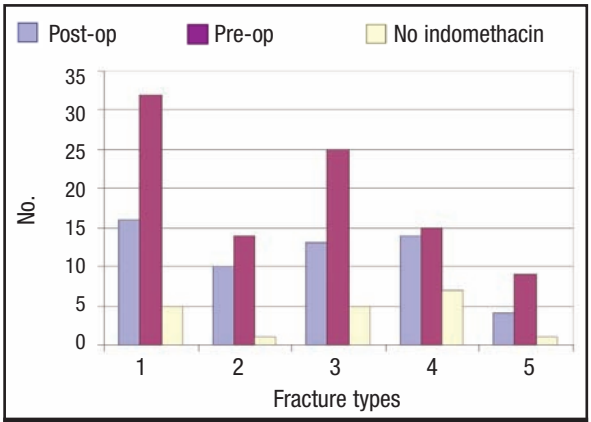

Figure 2: The administration of indomethacin in fractures, grouped into (1) posterior wall, (2) posterior column, (3) transverse, (4) both columns and (5) 'T' fractures

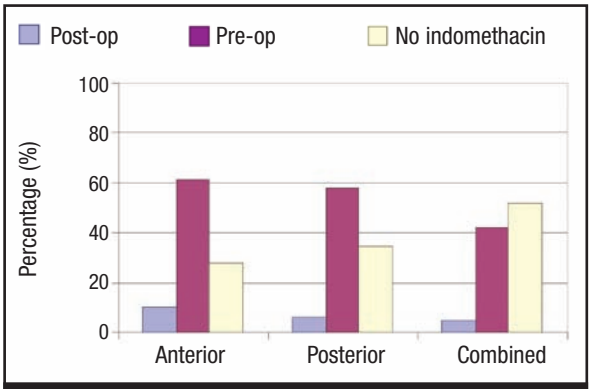

Figure 3: Indomethacin use in the anterior, posterior and combined approaches

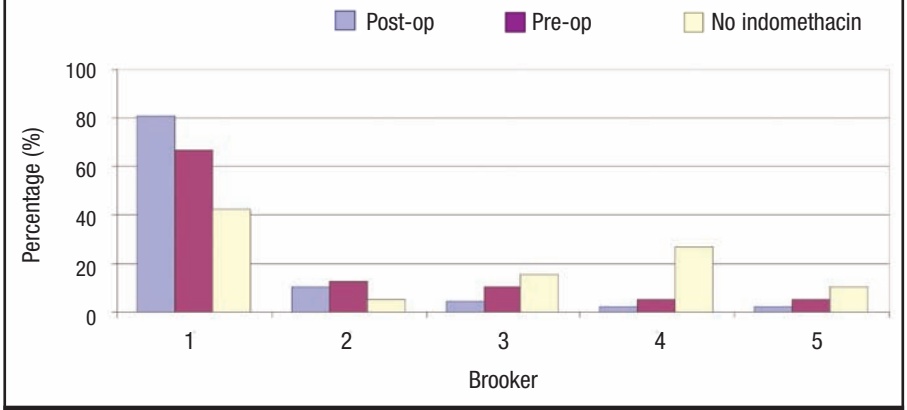

Figure 4: The incidence of heterotopic ossification as defined by the Brooker classification with differing indomethacin administration protocols

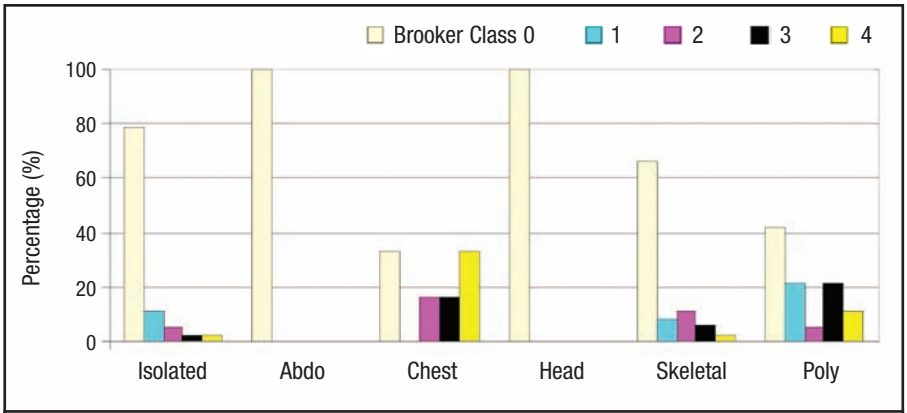

Figure 5: Associated injuries and the occurrence of HO

Statistical analysis

This was undertaken by the University's Medical Statistical department.

Results

The average ages were Group 1 (39 yrs); Group 2 (35 yrs); and Group 3 (37 yrs). The sex distribution was: male/female Group 1 (33/24); Group 2 (71/24); and Group 3 (12/7). The mechanism of injury, fracture types and surgical approach details are represented in *Figures 1, 2 and 3* respectively.

Figure 4 shows the percentages of the Brooker classes between the groups. The mean Brooker classes were Group 1 (0.7); Group 2 (0.3); and Group 3 (1.6). The p values when comparing these groups were Group 1 to Group 2 (p=0.04); Group1 to Group 3 (p=0.002); and Group 2 to Group 3 (p=0.000006). *Figure 5* gives the percentage of Brooker classes in the different types of associated injuries.

The average estimated blood losses were Group 1 (718 ml); Group 2 (508 ml); and Group 3 (1 238 ml).

The average number of days between injury and prior to surgery was Group 1 – 12 days (range 2-60); Group 2 – 9 days (1-25); and Group 3 – 13 days (1-59).

There were no fracture non-unions seen.

In the second week, one patient in Group 1 complained of gastrointestinal symptoms and the indomethacin was stopped.

There was no statistical correlation of the Brooker classes with age, sex, mechanism of injury, days to surgery, fracture classification or surgical approach.

The only aspect of the analysed data which correlated with the extent of HO formation was the presence of associated injuries. The presence of a concurrent chest injury or involvement of two or more systems increased the risk of HO severity *(Figure 5).*

HO of Brooker class 3 or 4 was recorded in 17 patients, six of 57 (10%) occurring in Group 1; four of 95 (4%) in Group 2; and seven of 19 (38%) in Group 3.

Eleven of these 17 had a loss of 20% of range of motion which defined them as clinically significant HO.

Further analysis of these 11 patients revealed that three patients redislocated post-operatively, three were polytraumas, three had chest injuries and the other two had no identifiable risk factors.

There were only two patients in Group 2 who had class 3 HO, of which one was polytraumatised, including a chest injury. Only two patients developed class 4 HO in the pre-operatively treated group (Group 2) and both of these had redislocated post-surgery.

Discussion

Chalmers,[4] following on the work of others such as Huggins and Urist, suggested that there are three requirements for bone formation to proceed: first an inducing stimulus, second an osteogenic precursor and third an environment permissive to osteogenesis. These three requirements are met immediately after damage to bone and soft tissue sustained at the time of injury with initiation of the ensuing inflammatory response, as demonstrated by Tonna who found new osteoblasts within 16 hours of fracturing rat femurs.[24]

Sawyer's review suggests that prostaglandins, among other mediators, are important in the differentiation of pluripotential cells and the proliferation of the resultant osteoblasts.[21,24] These prostaglandins are also important in the angiogenesis at the site of traumatised tissue.

Indomethacin, as an anti-prostaglandin, prevents or attenuates the process of differentiation and proliferation, thereby preventing HO. Ahrengart *et al* showed that a decrease in ectopic bone occurs in rats when indomethacin is used.[1] Tornkvist *et al* showed the same result in rats, but only if indomethacin was given either at the time of or before the induction process.[25] No benefit could be demonstrated if indomethacin was given after the first week. They also stated that indomethacin does not affect bone resorption – it only affects formation.

In support of Tornkvist's findings, in our series we encountered two patients with evidence of HO at the time of surgery, both occurring in Group 1. They were operated on at 6 and 19 days after injury. It was found that the tissues were abnormally firm to incise in the day 6 patient, and in the day 19 patient, new bone was encountered requiring excision. Later these cases developed class 4 and 2 HO respectively. Johnson *et al*[6] also reported HO encountered at the time of surgery. Their patient had bilateral acetabular fractures, and received indomethacin on day 20 after reconstruction of the first acetabulum. Fifteen days later when the other acetabulum was operated, HO was encountered. This did not progress after surgery.

Indomethacin has been shown to reduce HO in total hip replacements (THR),[7,8,22,23] with acetabular fracture surgery[6,9,13,14,20,25] and experimental studies.[1,4,25] However in the only published double-blind randomised study of 57 patients with acetabular fractures, Matta and Siebenrock could not show any statistical benefit with indomethacin.[12] Important however, is the fact that their patients only received indomethacin after the surgery and not before as in our Group 2 patients.

Radiation has also been shown to be effective in reducing the risk of HO in THR,[9,18,20,22] acetabular fractures[2,23] and experimentally.[25] This method is not logistically readily available to us, is more expensive and there is always the theoretical risk of carcinogenesis in this younger group of patients.[16] It is for these reasons that indomethacin is more attractive as a prophylaxis, and we were not happy to give our patients radiation.

In the light of the evidence supporting the concept that the HO process was initiated at the time of injury, and the experimental findings of Tornkvist suggesting that indomethacin administered at or soon after the induction process would be more effective in preventing HO, the senior author (GS) altered his policy to the administration of indomethacin as soon after injury as possible, providing patients were able to tolerate non-steroidal antiflammatory agents.

In our series a statistical reduction of the incidence and severity of HO was identified which appears to support this hypothesis. It also appears to document the benefit of even using indomethacin post-operatively in reducing the incidence and severity of HO as demonstrated in *Figure 4*.

The complications of using indomethacin for six weeks appear to minimal as found by others.[6,14,16,17] Fracture healing progressed at the expected rate and no fracture non-unions were recorded.

An unexpected finding in this study was the reduction of intra-operative and post-operative blood loss in the patients who had received indomethacin prior to surgery. While it is possible that this reduction could be as a result of the increased experience and surgical skill of the surgeon, we believe that the role played by indomethacin in reducing angiogenesis and the vascular component, thereby limiting blood loss, was significant. The relative importance of each of these factors is unknown and warrants further investigation.

Only one patient reported gastrointestinal symptoms (dyspepsia) and there were no documented gastrointestinal bleeds.

Age, sex and fracture type, which have been reported to show a relationship to the severity of HO,[5,14] did not appear to have one in our study. Contrary to reports by other authors,[5,6,9,14,19] the surgical approach, despite not being extensile, also did not show a relationship to the HO.

We, as have other authors,[2,5,17] found that polytraumatised patients and those with a chest injury, had an increased risk of severe HO. This may imply a significant soft tissue injury around the hip as well. Redislocation post surgery resulted in 100% clinically significant class 4 HO, as seen in two patients in Group 2. Whether this is due to the instability with irritation and inflammation of the tissues inducing a strong bone-producing response, or whether the severity of the soft tissue injury, which leads to the instability, results in

local cellular and/or humoral factors, is a matter for further study. We believe this to be a separate entity to the classically encountered HO.

Determining the final extent of HO that can be achieved earlier than previously thought is demonstrated in studies by Matta *et al*, McLaren *et al* and Moed *et al*.[10-14] In this series the Brooker class noted as early as six weeks and certainly at three months, did not change in severity when compared to subsequent follow-up.

This study is limited by its construction. Being a non-randomised longitudinal cohort study with a group of patients with one treatment regimen being followed by another on a different regimen does introduce an element of bias which is not controlled. The role of the surgeon's increasing technical expertise cannot be excluded. Assigning controls to 'not receiving indomethacin' was deemed unethical in the light of evidence suggesting the benefit of its administration. The cases not suitable for indomethacin treatment were included in this study to act to some extent as a control group. It is however acknowledged that these cases cannot be regarded as a true control group because of the biological or physiological differences they demonstrated by their sensitivity to indomethacin treatment.

Perhaps the ethical issue should be revisited in accordance with the findings of Matta *et al*.[12]

Conclusion

Polytraumatised patients and those with chest injuries appear to have an increased risk of developing HO. Redislocation is associated with a 100% risk of class 4 HO.

Indomethacin use in acetabular fracture surgery decreases the incidence and severity of HO. However if the indomethacin is given within one week of the injury, prior to surgery, and continued post-operatively there is even further benefit.

The content of this article and the preparation of this article is the sole work of the authors. In the absence of GS, HSR and JW are prepared to discuss the article in detail.

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