

Sagi HC, Jordan CJ, et al. Indomethacin prophylaxis for heterotopic ossification after acetabular fracture surgery increases the risk for nonunion of the posterior wall. J Orthop Trauma. 2014;28(7):377-83.

Design: Randomized clinical trial

Study question: Does indomethacin decrease the rate of occurrence of heterotopic ossification (HO) after acetabular fracture surgery, and does it affect the rate of nonunion when used in this manner?

Population/sample size/setting:

- 98 patients (71 men, 27 women, mean age 40.8) treated for acute acetabular fractures requiring operative treatment at a Level I trauma center in Tampa
- Eligibility criteria were a skeletally mature adult sustaining an acetabular fracture amenable to repair through a posterior approach, able to start taking indomethacin orally within one day of surgery
- Exclusion criteria included pregnancy, known contraindication to indomethacin, chronic NSAID use before injury, burn patients, and patients with head or spinal cord injury

Interventions and comparisons

- All patients had open reduction and internal fixation through a posterior approach, with débridement of necrotic muscle to reduce the occurrence of HO
- Randomized to one of four treatment regimens involving indomethacin or identical appearing placebo:
 - o Group 1 (n=26) took oral placebo for 6 weeks
 - o Group 2 (n=24) took 3 days of 75 mg of indomethacin and 5.5 weeks of placebo
 - o Group 3 took 1 week of daily 75 mg of indomethacin and 5 weeks of placebo
 - o Group 4 took 6 weeks of daily 75 mg indomethacin
- Compliance was assessed at 6 weeks by serum NSAID levels to ensure that group 4 was still taking indomethacin and that the other groups were not taking other NSAIDs

Outcomes:

- Patients underwent pelvic CT at 6 months to assess both HO and fracture union
 - o The volume of heterotopic bone was determined through computerized volumetric analysis

- An independent radiologist assessed fracture nonunion, which was defined as lack of bridging callus and visible fracture line on at least 3 contiguous axial cuts as well as coronal and sagittal reconstructed images
- Of the 23 patients in group 4, 16 had serum drawn for analysis, and 10 patients had detectable indomethacin for an estimated compliance rate of 63%
 - 3 patients in group 4 withdrew from the study because of GI complaints
 - No NSAIDs were detected in the patients in the other 3 groups
- 6 month CT was done in 21 patients in group 1, 17 in group 2, 17 in group 3, and 13 in group 4
- HO of any kind was seen on CT in 67% of group 1, 29% of group 2, 29% of group 3, and 69% of group 4, indicating equal occurrence of any kind of HO in groups 1 and 4 and equal occurrence in groups 2 and 3
- CT nonunion was seen in 4/21 patients in group 1, 6/17 in group 2, 4/17 in group 3, and 8/13 in group 4
 - Group 4 thus had greater incidence of nonunion than group 1 and equal incidence of HO
 - Group 3 had no greater incidence of nonunion than group 1 and had a lower incidence of HO
- Radiographic fracture union was associated with pain at 1 year, with VAS of 4 in patients with nonunion and VAS of 1 in patients with radiographic union

Authors' conclusions:

- This study supports the findings of other studies which did not show that indomethacin had a notable effect on HO after acetabular fracture surgery
- 6 weeks of indomethacin led to a significantly greater incidence of nonunion compared to placebo, and also to more withdrawals for GI side effects
- There was a high rate of attrition in all groups from the time of randomization to the time scheduled for the 6 month CT followup, and this may weaken the findings of the study and make its results less certain
- The indomethacin group had fairly poor compliance (63%) with taking the assigned medication
- Nevertheless, 6 weeks of indomethacin prophylaxis for the prevention of HO is not indicated for patients with acetabular fractures undergoing surgical repair
- 1 week of 75 mg of daily indomethacin may reduce HO compared to placebo without increasing the rate of nonunion

Comments:

- Table 2 shows differences in the mean volume of HO between the treatment groups, but these differences are not explained or interpreted by the authors

- Statistically, the incidence of HO and of nonunion are equal in group 2 (3 days of indomethacin) and in group 3 (7 days of indomethacin)
 - o Although it would be a post hoc analysis, groups 2 and 3 could be combined as “a short course of postoperative indomethacin” and this would create a group with a lower risk of HO and no greater risk of nonunion compared with placebo
- The high rate of noncompliance with 6 weeks of indomethacin does not necessarily weaken the inference that indomethacin increases the risk of nonunion, since there could have been more nonunions if group 4 had had full compliance with indomethacin for a full 6 weeks
- Many patients did not return for the scheduled 6 month CT scan, and their characteristics are not predictable, but the authors are likely to be correct in speculating that patients with more symptoms are more likely to return for followup imaging procedures

Assessment: adequate for some evidence that a postoperative course of 75 mg of daily indomethacin does not reduce the risk of heterotopic ossification compared to placebo, and that the risk of nonunion may be increased with 6 weeks of indomethacin.

Not for evidence:

A short course of 3 to 7 days of postoperative indomethacin may reduce the risk of heterotopic ossification without increasing the risk of nonunion. (for task force to discuss)