Celecoxib Versus Indomethacin in the Prevention of Heterotopic Ossification After Total Hip Arthroplasty

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Abstract: A cyclo-oxygenase (COX)-1 and COX-2 inhibitor (indomethacin) and a selective COX-2 inhibitor (celecoxib) were compared in the prevention of heterotopic ossification after total hip arthroplasty. In 250 patients receiving indomethacin and in 150 patients receiving celecoxib for 20 days after surgery, an overall incidence of heterotopic ossification of 17.5% and 14.3% was seen, respectively (difference not statistically significant: $P > .05$). No grade III or IV ossifications were seen in either group. Twenty-one patients in the indomethacin group (8.4%) and 3 patients in the celecoxib group (2.0%) required treatment discontinuation, because of side effects ($P < .05$). Celecoxib, a selective COX-2 inhibitor, shows the same efficacy as indomethacin in the prevention of heterotopic ossification after hip prosthesis with significantly fewer side effects. **Key words:** celecoxib, indomethacin, COX-2, heterotopic ossification, hip prosthesis, total hip replacement.

Heterotopic ossification may occur after total hip arthroplasty [1] or other surgical procedures or trauma around the hip [2–4]. Etiopathogenesis of ectopic bone formation after hip trauma or surgery remains unclear. Friedenstein [5] hypothesized that migrated cells from bone marrow could change connective tissue in osteogenesis. Ackermann [6] and Collins and Stone et al. [7] favored the idea that muscle lesions or interstitial hemorragic foci could lead to muscle degeneration, proliferation of perivascular connective tissue, and finally to bone metaplasia. Urist and McLaren [8] believed that a lesion of the periostium could cause a differentiation of the osteogenetic cells and the occurrence of periarticular bone formation. Whatever the etiopathogenesis is, after total hip arthroplasty heterotopic ossifications can occur at a rate ranging from 14% to 63%, and in 2% to 13% of cases, according to different authors [1,9–13], the extensive formation of ectopic bone can be painful and significantly reduce joint motion and function, and it can make complex surgical procedures necessary to remove the ossified tissue [14].

Risk factors for developing ectopic ossifications include previous surgeries, a history of hypertrophic osteoarthritis, ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis, and extensive hip trauma [13,15]. Unfortunately these predisposing factors, which can raise the risk of developing ectopic ossification by four times, cannot be used to select patients suitable for prophylaxis. In fact, the risk of this complication, even in the general pop-

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Table 1. Age and Gender Distribution in Groups 1 and 2

	Mean Age (n)	Gender (% of Women)
Group 1 (n = 250)*	62.3	72%
Group 2 (n = 150)†	59.3	73.5%

*Patients treated with indomethacin.
†Patients treated with celecoxib.

ulation, remains so high that mandatory prophylactic treatment seems important in all patients undergoing total hip arthroplasty and, more generally, in hip surgery or trauma.

A variety of treatments have been attempted to prevent the occurrence of ectopic ossifications after hip surgery. Nonsteroidal anti-inflammatory drugs like indomethacin and other aspirin-like drugs, which act by inhibition of the enzymes cyclooxygenase (COX)-1 and COX-2, have been successfully used after total hip arthroplasty [16–20], after Chiari osteotomy of the pelvis [2] and in acetabular fractures [4]. Low-dose irradiation after total hip arthroplasty has also been reported to be effective in the prevention of periarticular ossification [21,22]. Although an extensive use of low-dose irradiation is limited by logistic problems, costs, and concerns about irradiating a vast population of patients, the use of non-steroidal anti-inflammatory drugs is an easy to do and effective prophylaxis that can be performed in any hospital, even if side effects can limit its use [17].

Selective COX-2 inhibitors are a new class of anti-inflammatory drugs that have been shown to selectively inhibit the COX-2 enzyme, while leaving the COX-1 function intact. This allows a significant reduction in the occurrence of side effects, especially on the gastrointestinal tract and on platelet function, while preserving the anti-inflammatory action of the drug [23–25]. To our knowledge, this is the first study that compares the effectiveness and safety of a COX-2 inhibitor, celecoxib, with a COX-1 and COX-2 inhibitor, indomethacin, in the prevention of heterotopic ossification after total hip arthroplasty.

Material and Methods

This study included 400 patients affected by coxarthrosis and undergoing surgery to implant a noncemented total hip arthroplasty at the Gaetano Pini Institute of Milano. In all the cases, a direct lateral transgluteal approach, without trocantherotomy, was used. Exclusion criteria were previous surgery on the same hip, ankylosing spondilitis, diffuse idiopathic skeletal hyperostosis, and neurologic diseases, all conditions that are suspected to increase the risk of development of heterotopic ossification [13,15].

All patients received a low-weight heparine, sodium enoxaparin, 4,000 IU/d and ranitidil 150 mg × 2/d for 30 days after surgery. The patients were divided into 2 groups and prospectively evaluated. The first group of 250 patients received indomethacin 50 mg × 2/d. Starting the day after the intervention and for 2 days postoperatively, indomethacin was administered rectally and then orally until day 20 after surgery. The second group included 150 patients who received celecoxib 200 mg × 2/d, starting 2 days after surgery and for 20 days postoperatively. The 2 groups were similar in age, gender (Table 1) and preoperative diagnosis (Table 2).

Heterotopic ossification was evaluated by a radiologist and an orthopedic surgeon blinded to the treatment the patient received. Grading of heterotopic ossification was performed using anteroposterior radiographs of the hip at 12 months after surgery, according to the classification of Brooker and Bowerman [1]. This system classifies the absence of heterotopic bone formations, as grade 0, the presence of islands of bone within the soft tissues of the treated hip as grade I, the occurrence of bone spurs and a gap between opposing bone surfaces of $\geq$1 cm as grade II, the presence of bone spurs and a gap of $<$1 cm as grade III, and a bridge of bone across the joint as grade IV. Heterotopic ossification of grade III or more is associated with increasing impairment of range of motion and function [1]. For statistical analysis of the data, the chi-square test was used. P values $< .05$ were considered significant. Patients for whom the treatment was stopped because of the occurrence of side effects were not included in the statistical evaluation of heterotopic bone formation.

Table 2. Preoperative Diagnosis in Groups 1 and 2

	Idiopathic Coxarthrosis	Dysplastic Coxarthrosis	Femoral Head Necrosis	Other
Group 1 (n = 250)*	38%	49%	8%	5%
Group 2 (n = 150)†	34%	53%	9%	4%

*Patients treated with indomethacin.
†Patients treated with celecoxib.

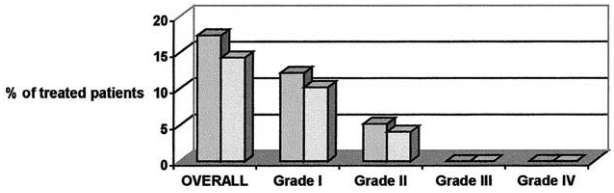

Fig. 1. Incidence of heterotopic ossification in group 1 (■; patients treated with indomethacin) and in group 2 (□; patients treated with celecoxib) according to Brooker's classification. Differences are not statistically significant ($P > .05$).

Results

Heterotopic ossifications developed in 40 patients (17.5%) who completed the indomethacin treatment. Grade I ossifications were seen in 28 patients (12.2%), and grade II in 12 patients (5.2%). Heterotopic ossification developed in 21 patients (14.3%) who completed the celecoxib treatment. Grade I ossifications were seen in 15 patients (10.2%), and grade II in 6 patients (4.1%). The difference in the incidence of heterotopic ossifications between the 2 groups was not statistically significant ($P > .05$). No grade III or IV ossifications were seen in either group (Fig. 1).

In the indomethacin group 21 patients (8.4%) required treatment discontinuation after a mean 9.5 days of therapy, because of gastrointestinal side effects (16 patients), excessive bleeding (4 patients), or mental confusion (1 patient). In the celecoxib group, 3 patients (2.0%) reported nausea or gastrointestinal pyrosis that required treatment discontinuation after 14 days of treatment in the average. The difference in the rate of discontinuation because of side effects was statistically significant ($P < .05$) (Table 3). No radiologic signs of early aseptic loosening of hip prosthesis were seen in either group at the time of follow-up evaluation.

Discussion

We believe that prophylaxis of heterotopic bone formation is today a mandatory part of the treatment of every patient who undergoes hip surgery, particularly after total hip arthroplasty. In fact, even if risk factors for developing ectopic ossification are well known [13,15], as stated by Kolbl and Knelles et al. [22], "on an absolute scale considerably more patients without risk factors develop heterotopic ossification because the number of patients with risk factors is low compared to all patients receiving total hip replacement. In this respect, prophylactic treatment after total hip replacement seems advocated for all patients."

Although radiation therapy has been shown effective in several studies [21,22], logistic considerations, costs, and concerns about large-scale irradiations favor the use of pharmacologic prophylaxis. Indomethacin efficacy in reducing ectopic bone formation after total hip arthroplasty and in hip surgery and trauma has been well recognized in many different studies [2,4,16–20]. Adverse effects associated with COX-1 and COX-2 inhibitors are not negligible, especially for older patients who often have associated cardiovascular, gastrointestinal, or other pathologic conditions [17]. Selective COX-2 inhibitors appear to have a more safe profile of use, especially concerning gastrointestinal and platelet function [23–25].

In this study, celecoxib, a highly selective COX-2 inhibitor, showed the same efficacy as indomethacin for preventing heterotopic ossification after total hip arthroplasty with significantly fewer side effects and a lower rate of discontinuation. To our knowledge, this is the first study that shows the efficacy and safety profile of celecoxib in preventing heterotopic bone ossification after total hip arthroplasty compared with a COX-1 and COX-2 inhibitor. Zacher, Walther, and Gursche [26] recently reported briefly on the efficacy of rofecoxib, 25 mg daily, in the prevention of heterotopic ossification after total hip arthroplasty compared with data from the literature. Rofecoxib and celecoxib are both selective COX-2 inhibitors. Compared with rofecoxib, celecoxib has been recently shown to be less prone to cause hypertension and peripheral edema in a very large observational study [27]. Therefore, it appears be more suitable for extensive use in the prevention of heterotopic ossification in patients undergoing total hip arthroplasty who are older and affected by cardiovascular pathologies.

Table 3. Treatment Discontinuation Because of Side Effects in Groups 1 and 2

	Treatment Discontinuation (%)‡	Treatment Time Before Discontinuation (d)
Group 1 (n = 250)*	8.4%	9.5
Group 2 (n = 150)†	2.0%	14

*Patients treated with indomethacin.
†Patients treated with celecoxib.
‡Differences are statistically significant ($P < .05$).

Indomethacin acts by inhibiting COX-1 and COX-2, which are needed for the production of prostaglandins [28]. The role of prostaglandins E and F in fracture-healing and in bone metabolism has been described [29,30]. Indomethacin may also inhibit the differentiation of preosteoblasts [31]. These activities probably explain the effectiveness of this drug in preventing ectopic bone formation after surgery or trauma. A recent report highlights the effect of COX-2 selective inhibitor's on bone growth in an *in vivo* animal model [32]. In this experimental set, the suppression of the bone formation was explained either by an inhibition of the initial inflammatory stages associated with bone growth or by the direct effect of COX-2 inhibition on mesenchymal cell and osteoblast proliferation, differentiation, or maturation. The present study provides indirect clinical evidence that selective inhibition of COX-2 is also effective in preventing ectopic bone formation after surgical hip trauma in humans.

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