Celecoxib and Heterotopic Bone Formation After Total Hip Arthroplasty

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ABSTRACT

We assessed the effectiveness of celecoxib in the prevention of heterotopic ossification (HO) following primary total hip replacement (THR). We studied 170 consecutive THRs. Sixty-three patients received celecoxib after surgery (200 mg twice/daily) for 28 days and 84 did not. HO was more common in non-celecoxib patients than in the celecoxib-group at 3, 6, and 12 months (P = 0.005, 0.004 and 0.01, respectively). At 1 year, fewer celecoxib recipients had Brooker classes II or III. None of the celecoxib patients developed HO Brooker class IV, while 2% in the non-celecoxib group did. No patient discontinued treatment or had revision for aseptic loosening. A short course of celecoxib for pain aids in the prevention of HO after primary THR, and could be a useful and safe option that does not interfere with anticoagulation.

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First described in 1883 by Reidel, HO is a common complication of THR [1–3]. Although the etiology of HO is unknown, numerous factors have been associated with an increased prevalence after THR including male gender, hypertrophic osteoarthritis, ankylosing spondylitis, previous history of HO, and revision THR. Previous reports have documented a wide variation in the incidence of HO after THR, ranging from 8% to 90% [4–7]. Severe HO has been associated with pain in the affected joint and decreased range of motion in 3% to 10% of patients after THR [3,8–10]. Therefore, the prevention of HO remains important in order to optimize outcomes for patients undergoing THR.

Multiple studies have suggested that non-steroidal anti-inflammatory drugs (NSAIDs) are effective in the prevention of ectopic bone formation after THR [11–13]. The exact mechanism of action of NSAIDs on bone formation remains unclear. These agents inhibit the two isoforms of the cyclooxygenase (COX-1, COX-2) enzyme preventing the transformation of arachidonic acid into prostaglandins and thromboxanes. Selective COX-2 inhibitors significantly reduce the occurrence of NSAIDs side effects, especially on gastroduodenal toxicity and platelet aggregation while preserving the anti-inflammatory effect [14,15]. The first aim of this retrospective study was to determine if a short course of celecoxib reduced the incidence of HO in comparison to a control group that did not take celecoxib at 3, 6, and 12 months after surgery. The second objective was to determine the influence of age, sex, and body mass index on the development of HO one year after surgery. Our third objective was to determine the association between taking celecoxib and severity of disease at 3, 6, and 12 months after surgery.

Materials and Methods

From May 2003 to June 2009, 497 primary THR on 440 consecutive patients with a mean age of 66.4 years old (range: 18.5–95.1) were performed by a single surgeon (CJL). End-stage osteoarthritis was the primary diagnosis in 358 cases (72%), avascular necrosis of the femoral head in 83 (16.7%), femoral neck fracture in 25 (5%), rheumatoid arthritis in 24 (4.8%) and other in 7 (1.4%). In our institution, the use of celecoxib postoperatively for 2 weeks started on July 1, 2005. Prior to this date, patients only received opioids and non-selective NSAIDs as needed. On December 19, 2007, the length of use of celecoxib changed to 4 weeks postoperatively. For this study we included those patients who did not use celecoxib postoperatively and those patients with postoperative use of celecoxib 200 mg twice a day for 4 weeks. Patients who did not have a complete radiographic evaluation of the involved joint preoperatively, and at 3, 6 and 12 months follow-up were excluded. One-hundred and eighty-nine patients (209 THRs) received celecoxib for 2 weeks, and 104 patients (118 THRs) with incomplete radiographic evaluation were excluded. Institutional Review Board was obtained before the beginning of this study.

One-hundred and forty-seven patients (170 THRs) [mean age at procedure: 64 years (range: 18.5–89.7); 62% female; 93% White; and 62% Hispanic] were included in the study. Of these, 63 patients (72 THRs) received celecoxib 200 mg twice daily for 4 weeks after primary THR and 84 patients (98 THRs) did not. All the patients underwent THR via a modified direct lateral approach (Hardinge). All patients received a tapered stem, and an uncemented press-fit technique was used for the...
femoral and the acetabular components. Screws were used in the acetabular component for supplemental fixation in all patients. All patients received prophylaxis for deep venous thrombosis with postoperative pneumatic compression devices initiated immediately after surgery, and oral anticoagulation (warfarin) for 4–6 weeks after surgery. In addition, as part of a multimodal pain management protocol, patients were allowed to take acetaminophen when necessary. Full weight bearing was permitted as tolerated on postoperative day 1. An abduction pillow was indicated at all times whenever in bed. Physical therapy was initiated in the afternoon if the patient was operated in the morning or the next day if the patient was operated after midday. Physical therapy was supervised by a licensed professional, and patients received treatment two times per day on 30-minute sessions as tolerated. Physical therapy consisted of transfer training, gait training with the use of a standard walker, bed mobility education, and general therapeutic exercises such as range of motion and manual resistive exercises. Most patients were discharged home within 3 to 4 days in the absence of complications.

Imaging consisted of a non-weight bearing anteroposterior and lateral radiographs of the involved hip and anteroposterior radiograph of the pelvis. All radiographs were evaluated for the presence of HO by two blinded investigators according to the Brooker classification [1]. Brooker class I: islands of bone within the soft tissue about the hip; class II: bone spurs from the pelvis or proximal end of the femur, leaving at least one centimeter between opposing bone surfaces; class III: bone spurs from the pelvis or proximal end of the femur, reducing the space between opposing bone surfaces to less than one centimeter; and class IV: apparent bone ankylosis of the hip. In our study, the two investigators were blinded as to the treatment regimen given to the patient. In a small pilot study with a sample of 20 patients the reliability between raters was strong [Spearman Rho = 0.84; P < 0.0001] for the Brooker classification at 1 year.

Fisher’s exact test was used to evaluate the association between taking celecoxib and the development of HO at 3, 6, and 12 months. Statistical modeling was completed using a multi-nomial regression to evaluate the influence of gender, BMI, and age at procedure on the incidence of HO at one year. Contingency tables were created to assess the association between severity of disease based on the Brooker classification and taking celecoxib at 3, 6, and 12 months using a chi-square test of independence. Fisher’s exact test was used to evaluate the association between sex and incidence of HO. Alpha was set at 0.05.

**Results**

Overall, heterotopic ossification was detected in 95 (55.8%) hips. The incidence of HO was lower in the group that received celecoxib. Heterotopic ossification was more common in the group that did not receive celecoxib at 3 months (37% vs. 22%; P = 0.005), 6 months (52% vs. 33%; P = 0.004) and 1 year (64% vs. 44%; P = 0.01).

Age, sex, and BMI together significantly predicted HO (P = 0.002) at 1 year post-op. However, evaluating individual parameters, sex (P = 0.005; B = −0.97) and BMI (P = 0.01; B = 0.08) were significantly contributors to the model while age was not (P = 0.18; B = −0.01). There was no difference in age between those who did and did not develop HO (P = 0.19). Pertaining BMI, those who did not develop HO at 1 year had a higher BMI of 29.2 kg/m² (17.5–46.9) compared to those who developed HO that had a BMI of 26.4 kg/m² (18.4–37.7).

Evaluating severity of disease, individuals who did not take celecoxib had greater severity of disease based on the Brooker classification at three months post-operatively (P = 0.004). Results were similar at six months; those who did not take celecoxib were associated with greater disease severity (P = 0.004). By one year, not taking celecoxib remained associated with having greater disease severity. Two percent of patients in the group not taking celecoxib had Brooker class IV. No class IV was seen in those patients who received celecoxib (Table).

One year after THR, men had a significantly greater incidence of HO (69%) when compared to women (48%) (P = 0.01). At one year, 58% percent of men who developed HO received celecoxib while only 33% of women who developed HO received celecoxib (P = 0.04). Interestingly, 81% of men who did not receive celecoxib developed HO, compared to 57% of women who did not take celecoxib (P = 0.02). Adjusting for gender; by one year, 58% of men taking celecoxib had at least a Brooker class 1, compared to 33% of women (P = 0.04). Severity of disease was not associated with not taking celecoxib when accounting for gender (P = 0.08).

There were four revisions. All four patients did not receive celecoxib postoperatively. Of these, three were caused by late deep infection and one by a femoral fracture 7 years postoperatively. None of the patients who received celecoxib required treatment discontinuation. There were no radiographic signs of aseptic loosening in any group at the time of follow-up evaluation.

**Discussion**

Heterotopic ossification is a common finding after THR that may be associated with pain and reduced range of motion with the need of further complex surgery in few very severe cases. Although the mechanism involved in the formation of HO has not been fully elucidated, the usefulness of nonsteroidal anti-inflammatory drugs in HO prevention suggests that prostaglandins may play a key role. In our study, a short course of celecoxib was associated with a lower incidence of HO after THR. Further, men had both greater incidence and severity of HO than women.

Non-steroidal anti-inflammatory drugs have successfully reduced the incidence of HO after THR. Adverse reactions are associated with the use of non-selective NSAIDs. Gastrointestinal and bleeding complications are common among users of these agents [14,15]. This may increase the risk of treatment discontinuation and could interfere with thromboprophylaxis after THR. In a study comparing celecoxib vs. indomethacin for the prevention of HO [16], the authors reported that a significantly greater number of patients in the indomethacin group had to discontinue treatment as a result of the excessive bleeding and gastrointestinal side effects. On the other hand, COX-2 inhibitors have been related with increased cardiovascular risk [17–19]. Although a large randomized double-blind trial [15] and several large observational studies [20–22] with celecoxib have demonstrated no difference in cardiovascular risk compared with non-selective NSAIDs, other studies have found an increase in cardiovascular events in patients taking celecoxib for at least 12 months [23,24]. Recently, the Cross Trial Safety Analysis [25], a National Cancer Institute commissioned meta-analysis of 6 randomized, placebo-controlled trials to analyze the cardiovascular safety of celecoxib, found evidence for differences in risk based on the dose

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FUP, follow-up; 3 M, three months; 6 M, six months; 12 M, twelve months.

**Table**

Incidence and Severity of Heterotopic Ossification According to Treatment Group.

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regimen of celecoxib. Although in our study celecoxib was used in a lower dose for a short-term, caution should be exercised in patients susceptible to cardiovascular events. While some studies have reported mixed results with the use of COX-2 inhibitors (e.g., rofecoxib, meloxicam) in HO prophylaxis [26–29], there is little information on the use of celecoxib in patients for the prevention of HO. To our knowledge, only two other studies have assessed this effect of celecoxib [16,30]. In 2004, a group in Italy [16] reported no significant difference in the incidence of HO between celecoxib and indomethacin 1 year after THR (14% vs. 17%, respectively). In a prospective, randomized trial [30], performed in Switzerland, celecoxib was more effective than ibuprofen in preventing HO 3 months following THR (41% vs. 60%, respectively). In our study, incidence of HO was 22% and 37% at 3 months and 44% and 64% at 1 year, for those who received celecoxib and those who did not, respectively. While the preceding studies showed that celecoxib effectively decreased the occurrence of HO, there is large variation in the incidence among celecoxib dose regimens. In the first study [16], celecoxib was administered 200 mg twice a day for 20 days. In the second study [30], celecoxib was prescribed at the same dose but for 10 days. In our study, celecoxib was administered 200 mg twice a day for 28 days postoperatively. This may indicate that dose and time of administration may play a role in the formation of HO.

Our study has several limitations. First, this is a retrospective study and selection bias cannot be excluded, which could account for the higher than expected incidence of HO in both groups. There were more men in the group that received celecoxib than those who did not (46% and 32%, respectively), but the discrepancy in gender distribution across treatment groups did not reach statistical significance (P = 0.06). Several studies have determined that male gender is a risk factor for HO [31–33]. Based on this observation, women predominance in the group that did not receive celecoxib should have favored a lower incidence of HO in this group. The significantly higher incidence of HO in the group that did not receive celecoxib gives further support to the role of celecoxib as a prophylactic agent for HO. Second, the Brooker classification has limitations in terms of reliability and reproducibility; however both observers in our study, blinded to the treatment group, had good to strong reliability coefficients. Lastly, we noted a reduction in the incidence of HO after THR using a modified Hardinge direct lateral approach, and for this reason, the effect may not be extrapolated to other approaches.

In conclusion, our results demonstrate that celecoxib helps to prevent HO. A short course of celecoxib after primary THR could be a safe and useful pain treatment option that does not interfere with anticoagulation and has the secondary benefit of helping in the prevention of HO following THR. Other research studies have shown conflicting data about the effects of celecoxib on HO. This discrepancy in the existing research suggests that differences in dose and time of administration may be responsible for the differences in the effectiveness of celecoxib in reducing incidence of HO. Larger prospective, randomized controlled trials with celecoxib used at higher doses and aimed to reduce HO may answer this question.

Acknowledgments

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References