Instructions

1. Review the stated learning objectives at the beginning of the CME article and determine if these objectives match your individual learning needs.
2. Read the article carefully. Do not neglect the tables and other illustrative materials, as they have been selected to enhance your knowledge and understanding.
3. The following quiz questions have been designed to provide a useful link between the CME article in the issue and your everyday practice. Read each question, choose the correct answer, and record your answer on the CME REGISTRATION FORM at the end of the quiz.
4. Type or print your full name and address and your date of birth in the space provided on the CME Registration Form.
5. Indicate the total time spent on the activity (reading article and completing quiz). Forms and quizzes cannot be processed if this section is incomplete. All participants are required by the accreditation agency to attest to the time spent completing the activity.
6. Complete the Evaluation portion of the CME Registration Form. Forms and quizzes cannot be processed if the Evaluation portion is incomplete. The Evaluation portion of the CME Registration Form will be separated from the quiz upon receipt at ORTHOPEDICS. Your evaluation of this activity will in no way affect the scoring of your quiz.
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8. Your answers will be graded, and you will be advised whether you have passed or failed. Unanswered questions will be considered incorrect. A score of at least 80% is required to pass. If a passing score is achieved, Vindico Medical Education will issue an AMA PRA Category 1 Credit™ certificate within 4-6 weeks.
9. Be sure to mail the CME Registration Form on or before the deadline listed. After that date, the quiz will close. CME Registration Forms received after the date listed will not be processed.

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COX-2 Inhibitors for the Prevention of Heterotopic Ossification After THA

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As a result of reading this article, physicians should be able to:

1. Recognize the increased possibility of heterotopic ossification after total hip arthroplasty (THA).
2. Outline the increased percentage of serious complications with the use of conventional nonsteroidal anti-inflammatory drugs (NSAIDs).
3. Identify a safer drug for prophylaxis of heterotopic ossification after THA.
4. Recognize that the risk of side effects with COX-2 inhibitors is lower compared to conventional NSAIDs and directly related to the time of administration.

ABSTRACT
Nonsteroidal anti-inflammatory drugs (NSAIDs) may prevent heterotopic ossification after total hip arthroplasty (THA). Cyclooxygenase 2 (COX-2) inhibitors may minimize side effects. The goal of this review was to compare the effectiveness and side effects of the perioperative use of selective COX-2 inhibitors with those of conventional NSAIDs in patients undergoing THA. We followed the systematic reviews’ updated methods of the Cochrane Collaboration Back Review Group and searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials. We identified all...
randomized controlled trials until April 2009 enrolling THA patients and comparing COX-2 inhibitors to NSAIDs. We assessed their methodological quality and extracted data. Five randomized controlled trials were included. Prevention of heterotopic ossification and side effects with COX-2 inhibitors were significant in 2 studies. Discontinuation for side effects was not significant. COX-2 inhibitors do not prevent heterotopic ossification after THA significantly better than conventional NSAIDs, while they are advantageous regarding side effects.

Heterotopic ossification, sometimes referred to as ectopic ossification or heterotopic bone formation, is the formation of mature lamellar bone in nonosseous tissues and is a frequent complication following total hip arthroplasty (THA). The precise pathogenesis is unknown, but surgical trauma to soft tissue or bone appears to induce the process. It has been estimated that between a quarter and two-fifths of all patients undergoing elective THA will develop heterotopic ossification. For most of these patients, heterotopic ossification is mild to moderate in extent, but in a few cases it is severe. Risk factors for heterotopic ossification after THA include hypertrophic osteoarthritis, male sex, age older than 60 years, diffuse idiopathic skeletal hyperostosis, heterotopic ossification in the ipsilateral or contralateral hip, and ankylosing spondylitis. The most common and by far the most important symptom of severe heterotopic ossification (Brooker stages III and IV) is the limitation of range of motion (ROM) of the involved joint.

Two prophylactic therapy options exist for heterotopic ossification: irradiation of the surgical field and the use of nonsteroidal anti-inflammatory drugs (NSAIDs). A 1996 study suggested preoperative irradiation for the prevention of heterotopic ossification following THA to eliminate the discomfort and morbidity associated with conventional postoperative treatment. Of particular importance is the oncogenic risk imposed by radiation therapy. However, to our knowledge, no reports exist of neoplasms or cancers after hip radiation, even in larger doses, in series using it for heterotopic ossification prevention.

Several studies have provided evidence for the high efficacy of NSAIDs in preventing heterotopic ossification after THA. The beneficial action of NSAIDs for prophylaxis against heterotopic ossification is attributed to the inhibition of cyclooxygenase 2 (COX-2) enzyme, an inducible enzyme in the osteoblasts. COX-2 is the enzyme that catalyzes the first reaction of arachidonic acid toward prostaglandin formation. The increased concentration of prostaglandins, especially PGE2, results in new bone matrix production and thus in heterotopic ossification formation. These prostaglandins are also responsible for inflammation and pain. Concurrently, prostaglandins’ synthesis by cyclooxygenase 1 (COX-1), a constitutive enzyme, is inhibited when conventional NSAIDs are being ingested. These prostaglandins are among other functions responsible for maintenance and protection of the gastrointestinal tract. As a result of this inhibition, increased risk of serious side effects, most notably gastrointestinal, may occur with ingestion of conventional NSAIDs, even for only 1 week.

According to the medical literature, the percentage of side effects for indomethacin, the gold standard regarding prophylaxis against heterotopic ossification after THA with NSAIDs, is 37%. Also, a matter of great concern is excessive wound bleeding after perioperative administration of conventional NSAIDs. These detrimental side effects warrant a search for the use of alternative drugs that block only the activity of COX-2. This would prevent heterotopic ossification formation after THA without having the well-recognized toxic effects related to COX-1 inhibition.

The goal of this review was to compare the effectiveness and side effects of the perioperative use of selective COX-2 inhibitors with those of conventional NSAIDs in patients undergoing THA. The preference of selective COX-2 inhibitors may be crucial for these patients with a history of gastrointestinal problems.

**Materials and Methods**

**Review Design**

We identified all studies published until April 2009 using the review’s inclusion criteria and the updated method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group. The selected studies passed methodological quality assessment based on the Cochrane Bone, Joint and Muscle Trauma Group score for reporting of methodological quality.

**Criteria for Studies in This Review**

All randomized controlled trials comparing selective COX-2 inhibitors with NSAIDs for patients undergoing primary or revision THA were eligible for this review. All trials were considered regardless of the language of publication. The intervention under investigation was “any NSAID at any dose” vs “a selective COX-2 inhibitor.” The primary outcome measure was the development of heterotopic ossification as verified radiologically using the Brooker grade for heterotopic ossification of the hip. A binary system (heterotopic ossification present or absent) was used where the Brooker scale was not used to assess the outcome. The last recorded radiological measurement was used in the analysis. Data were also sought in the secondary outcome measures of late postoperative pain, decreased ROM and physical disability, death from any cause, cerebral infarction or stroke of unknown cause, cerebral hemorrhage, deep vein thrombosis, pulmonary embolism, hematoma or melena, excessive bleeding from the wound or drainage site, evacuation of hematoma, postoperative bleeding requiring transfusion, and gastrointestinal complications.
Search Methods for Study Identification

We performed a computer-aided search of the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases. The identification of studies to be included in this review was done using the following search strategy: (prophylaxis OR prevention OR inhibition OR prevents OR inhibits OR prevent OR inhibit) AND heterotopic ossification AND NSAIDs AND (cyclooxygenase 2 inhibitors OR COX-2 inhibitors OR COX-2 inhibitor OR celecoxib OR rofecoxib OR valdecoxib) AND (total hip arthroplasty OR total hip replacement).

Three reviewers (G.V., I.S., A.F.M.) assessed the methodological quality of the studies included in this review. The generic scheme together with the basic scoring criteria that was followed is given in The Cochrane Library 2007, Issue 4. All criteria were scored as yes, no, or unclear. The studies were considered to be of high quality if at least 6 criteria for internal validity, 3 descriptive criteria, and 1 statistical criterion were scored positively. The studies were considered to be of sufficient quality if at least 4 criteria for internal validity, 2 descriptive criteria, and 1 statistical criterion were met.

All citations identified by the search strategy were screened. Studies that conformed to the selection criteria were reviewed in detail, and if agreement occurred between the authors, all randomized controlled trials of a selective COX-2 inhibitor vs a conventional NSAID that reported the grade of postoperative heterotopic ossification at the hip were included. In case of disagreement not resolved by discussion, a fourth reviewer (P.J.P.) adjudicated. All data, including data on methodological quality, were collected independently by the 3 reviewers. Wherever possible, the published findings were confirmed and supplemented by communication with the principal study investigator. Information about randomized patients excluded from the published analyses was sought for inclusion in the analyses.

All analyses were conducted on dichotomous outcomes derived from tabular data. For each study, relative risks and 95% confidence intervals (CIs) were calculated and the results combined using a fixed effects model. These were displayed on forest plots. Heterogeneity between the results of both individual studies and, in the case of sensitivity analyses, between the results of combined trials were tested using a Cochran’s chi-square test.

RESULTS

Study Selection

Five publications were identified that met our inclusion criteria and had the methodological quality necessary for this review.1,3,18-21 Eight studies were primarily identified but excluded from the review (Table 1).3,18-21 Studies by Macfarlane et al’s 22 studies by Macfarlane et al’s 22-23 were primarily identified; however, since only randomized controlled trials were included in the design of this review, both of these studies were excluded. Studies by Buvanendran et al’s 24 and Franchin et al’s 25 compared the effectiveness of rofecoxib with a placebo group. Since in the review we included only trials containing any NSAID at any dose vs a selective COX-2 inhibitor, these studies were also excluded.

Fijn et al’s 26 addressed the prevention of heterotopic ossification after THA with NSAIDs. Barthel et al’s 27 compared indomethacin and meloxicam, but meloxicam is not a COX-2 inhibitor, having partial COX-2 specificity.30 Vastel et al’s 28 compared a selective COX-2 inhibitor and a conventional NSAID; however, total validity scoring was low (58.3%), and the study was completely inadequate in 5 out of 12 validity criteria, so it was excluded from the review, although the primary outcome is in accordance with that of the included trials. Finally, the computer-aided search of the Cochrane Central Register of Controlled Trials identified Persson et al’s 29 comparative study of patients receiving ibuprofen. Since ibuprofen is not a COX-2 inhibitor, this study was also excluded.

Methodological Quality of Included Studies

The articles by Grohs et al,18 van der Heide et al,19 and Romanò et al21 are the highest evaluated articles (91.6%) regarding their methodological criteria. Saudan et al’s 3 article was found to be of sufficient methodological quality (91.6%) regarding their methodological criteria. Saudan et al’s3 article was found to be of sufficient methodological quality (79.1%). In van der Heide et al’s20 second article, no major methodological statement was found, except the dosage and duration of the indomethacin group. This trial was found to be of sufficient methodological quality (62.5%) (Table 3).

Evaluation of the Prophylactic Effect of Selective COX-2 Inhibitors on Heterotopic Ossification vs Conventional NSAIDs

In the 5 included studies, there was a nonsignificant 23% reduction ($P=.150; 95% CI, 46%-10%) in the risk of het-

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Table 1

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Table 2

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Heterotopic ossification among patients who were administered COX-2 inhibitors. Among these studies, there were marked differences in the size of the observed effects of COX-2 inhibitors on heterotopic ossification, which ranged between an increase of 54% and a reduction of 66%.

Among these studies, there were marked differences in the size of the observed effects of COX-2 inhibitors on heterotopic ossification, which ranged between an increase of 54% and a reduction of 66%.

The effects of COX-2 inhibitors on heterotopic ossification among patients who were administered COX-2 inhibitors. There was no statistically significant heterogeneity among the studies ($P=.120$).

Overall, in the studies included in this review, 23 of 450 patients who received prophylaxis against heterotopic ossification with a selective COX-2 inhibitor had to discontinue the prophylactic treatment due to side effects, compared to 41 of 615 patients who had prophylaxis with conventional NSAIDs. The difference between the 2 treatments was not statistically significant (Figure 2).

**DISCUSSION**

In this review, we examined the current literature about the preventive use of selective COX-2 inhibitors against heterotopic ossification formation after THA in comparison with that of conventional NSAIDs. From the literature search up to April 2009, five articles were considered to be of sufficient methodological quality and were included. In these articles, it appears that this new subcategory of NSAIDs is equally efficient with conventional NSAIDs. In addition, although this was found to be not statistically significant, the patients that were administered selective COX-2 inhibitors had fewer side effects. Selectivity for COX-2 inhibition can halve the risk of peptic ulceration without affecting the other side effects, most notably the increased danger of renal failure in older hypertensive patients, a population in which arthritis and hypertension are common comorbidities. However, one can argue that this may be attributed to the small number of trials performed. We acknowledge this and conclude that more studies are needed to come to a definite conclusion.

The danger of renal hypertension in combination with the imbalance that favors platelet aggregation, which results into thrombus formation from COX-2 inhibitors, calls their safety into question. However, the increased incidence of cardiovascular and cardiorenal events associated with the use of rofecoxib or celecoxib becomes apparent only after 12 to 18 months of continuous treatment. Moreover, COX-2 inhibitors appear to result in less perioperative blood loss in comparison with blood loss associated with the use of indomethacin. This is particularly important in patients undergoing major surgical operations such as THA where prophylaxis for deep vein thrombosis is implemented as a rule for 5 to 6 weeks postoperatively. In the studies included in this review, none of the patients treated with a COX-2 inhibitor presented bleeding as a complication. On the contrary, in the study by Romanó et al., four patients who were administered indomethacin had to discontinue the prophylactic treatment due to excessive bleeding. In the included studies, none of the patients had to stop the treatment due to hypertension or other vascular side effect, complications that are feared when selective COX-2 inhibitors are prescribed. However, this may be attributed to the short-term use of the drug.
Based on our findings, selective COX-2 inhibitors play a role in the prevention of heterotopic ossification. However, they do not prevent heterotopic ossification statistically significantly better than conventional NSAIDs. In addition, when selective COX-2 inhibitors are used, there is a tendency toward a lower rate of side effects that would lead to the discontinuation of the prophylactic measurements against the appearance of heterotopic ossification after THA; however, this has also been found not statistically significant compared to conventional NSAIDs, and moreover, it can be attributed to the short duration of the time needed to treat patients undergoing THA. Due to the small number of clinical studies, the effects and side effects of selective COX-2 inhibitors need to be proved in a large-scale review to determine the balance of benefits and risks for all outcomes and to draw a firm conclusion.

REFERENCES
