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Effect of Naproxen Prophylaxis on Heterotopic Ossification Following Hip Arthroscopy

A Double-Blind Randomized Placebo-Controlled Trial

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Background: Heterotopic ossification (HO) is a known complication of hip arthroscopy. Our objective was to determine the effect of postoperative naproxen therapy on the development of HO following arthroscopic surgery for femoroacetabular impingement.

Methods: Between August 2011 and April 2013, 108 eligible patients were enrolled and randomized to take naproxen or a placebo for three weeks postoperatively. Radiographs were made at routine follow-up visits for one year following surgery. The primary outcome measure was the development of HO, as classified with the Brooker criteria and two-dimensional measurements on radiographs made at least seventy-five days postoperatively (average, 322 days). The primary analysis, performed with a Fisher exact test, compared the proportion of subjects with HO between the treatment and control groups. A single a priori interim analysis was planned at the midpoint of the study.

Results: Our data safety and monitoring board stopped this study when the interim analysis showed that the stopping criterion had been met for demonstration of efficacy of the naproxen intervention. The prevalence of HO was 46% (twenty-two of the forty-eight in the final analysis) in the placebo group versus 4% (two of forty-eight) in the naproxen group ($p < 0.001$). Medication compliance was 69% overall, but it did not differ between the naproxen and placebo groups. Minor adverse reactions to the study medications were reported in 42% of the patients taking naproxen versus 35% of those taking the placebo ($p = 0.45$).

Conclusions: In this trial, prophylaxis with naproxen was effective in reducing the prevalence of HO without medication-related morbidity.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

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Heterotopic ossification (HO) is recognized as one of the most common complications associated with hip arthroscopy, occurring in 0% to 44% of individuals who did not receive prophylaxis^{1,2}. It forms as a result of trauma to the soft tissues surrounding the joint, leading to an osteogenic response in the surrounding musculature³. This creates

histologically normal bone in abnormal locations. Prophylaxis targets biochemical mechanisms of heterotopic bone formation by (1) disrupting inductive signaling pathways, (2) altering osteoprogenitor cells in target tissues, and (3) modifying the environment so that it is less conducive to formation of heterotopic bone⁴.

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Prophylactic nonsteroidal anti-inflammatory drugs (NSAIDs) have become the recommended treatment strategy for HO prevention on the basis of several retrospective case series showing that their use resulted in large reductions in the prevalence of HO following hip arthroscopy⁵⁻⁷. Although there is mounting evidence to support prophylactic NSAID therapy following hip arthroscopy, the development of HO is multifactorial⁴. Consequently, there are potentially confounding explanations for the observed effects of NSAID prophylaxis in reported case series, including temporal variations in arthroscopic procedures, surgical techniques, and surgeon experience^{2,5}. Without randomization of subjects, it is difficult to account for these inherent biases in case series and observational studies.

The purpose of this study was to evaluate the effect of postoperative naproxen therapy on the development of HO. Our hypothesis was that NSAID prophylaxis with naproxen after hip arthroscopy would reduce the prevalence of HO compared with that seen in patients who took a placebo. Secondarily, we hypothesized that naproxen would be associated with more frequent side effects compared with a placebo.

Materials and Methods

Study Design

This study was conducted at an academic institution. All arthroscopic procedures were performed by a single surgeon (S.K.A.) with a high-volume hip arthroscopy practice. The institutional review board approved this study. All study participants provided written informed consent for inclusion in the study prior to enrollment. A data and safety monitoring board was established to review the study data at regular intervals. The study was registered at ClinicalTrials.gov with the identifier NCT01539447.

Patients were considered for inclusion in the study if they were between eighteen and eighty years of age; were scheduled for hip arthroscopy for femoroacetabular impingement including cam and/or pincer resection; had an American Society of Anesthesiologists (ASA) classification of 1, 2, or 3; understood the explanation of the protocol; and provided written informed consent. The diagnosis of femoroacetabular impingement was based on physical examination findings, including pain with the impingement maneuver, and radiographic abnormalities, including an increased alpha angle, an increased center-edge angle, and evidence of a labral tear on magnetic resonance imaging. Exclusion criteria included (1) a history of a major gastrointestinal bleeding event, (2) a history of renal impairment or a creatinine level of >1.5 mg/dL, (3) use of NSAIDs within forty-eight hours before surgery or in the perioperative period, (4) a need to use NSAIDs (with the exception of acetylsalicylic acid) following surgery, (5) a history of heterotopic ossification following surgery, (6) a prior hypersensitivity reaction to naproxen, (7) another procedure scheduled to be performed concomitantly with the hip arthroscopy, or (8) patient refusal to participate.

Study Interventions

Hip arthroscopy was performed using standard anterolateral and mid-anterior portals^{8,9}. Additional portals were made at the surgeon's discretion if required to perform the operation. Femoroplasty and/or acetabuloplasty were performed, using a 5.5-mm burr, as required according to the type of femoroacetabular impingement diagnosed: femoroplasty only was used for cam-type impingement; acetabuloplasty only, for pincer-type impingement; and both femoroplasty and acetabuloplasty, for mixed-type resections. Labral repair was performed when necessary using bioabsorbable suture anchors; suture limbs were passed between the labrum and the acetabular rim and retrieved through the labrum. Capsular repair, using multiple simple nonabsorbable sutures, was performed in all patients who had a capsulotomy. Standard general anesthesia was administered for all of the procedures. A postoperative fascia iliaca block was performed in the post-anesthesia care unit if requested by the patient following the proce-

dures. The use of any other NSAIDs during the perioperative period was prohibited in this study population for three weeks.

Randomization Procedures

Patients who consented at their clinic visit to participate in this study were randomized preoperatively on the day of their surgery to take either naproxen (500 mg) or a placebo twice daily for three weeks following surgery. The randomization key was generated using computer-generated random permuted blocks and was delivered, in a sealed opaque envelope, only to the pharmacist preparing the study medications. Once enrolled, patients were given a three-week supply of naproxen or placebo to take postoperatively; a central pharmacy distributed the tablets in a container labeled with the randomization number and the words "Study Medication" without any indication of the contents to the patient or research team. Forty-four tablets were supplied to allow for twice-daily dosing over the three-week period. The two additional tablets were supplied in the event that doses were inadvertently misplaced or discarded.

Study Measures

The primary outcome of this study was defined as the appearance of HO on postoperative radiographs. Secondary measures were side-effect data related to the study medication. All patients underwent a preoperative evaluation including anteroposterior pelvic and frog-leg lateral radiographs of the hip. Patient sex, age, and body mass index (BMI) and the surgical procedures performed were recorded. Postoperatively, patients were scheduled for routine follow-up at four weeks, three months, six months, and one year. Anteroposterior and lateral radiographs of the affected hip were routinely obtained at each visit. Two independent orthopaedic surgeons blinded to treatment allocation determined the presence of HO. In the event that they disagreed, the opinion of a musculoskeletal radiologist was enlisted. Radiographs were considered adequate for determining the presence or absence of HO if they had been obtained at least seventy-five days postoperatively². HO was classified according to the Brooker criteria, the largest two-dimensional measurement on either the anteroposterior or the lateral radiograph as previously described⁵, and the location relative to the hip joint (anterior or lateral).

At the first (four-week) postoperative visit, we documented the patient's adherence to the medication protocol by counting the tablets remaining in the medication container, which the patients had been instructed to bring with them. Patients were considered to have adhered to the therapy if they had missed fewer than five doses of the study medication. The attending surgeon also directly questioned the study participants about NSAID-specific side effects including gastrointestinal upset, nausea, vomiting, and gastrointestinal bleeding. Case-report forms were completed at the four-week follow-up visit to document any side-effects and other non-specified maladies or complications during the prescribing period whether they were thought to be study-related or not.

Statistical Analysis

Sample Size

The study sample size was calculated to provide adequate power based on the size of the hypothesized treatment effect, which reflected available data at the time of study initiation (2011). On the basis of published studies^{2,5-7} and our own experience at the time of study initiation, we estimated a 10% prevalence of HO following hip arthroscopy in patients who received the placebo and 2% in those who received the treatment drug. With the hypothesis of a similar difference between the two randomized groups, it was calculated that 149 patients in each group would provide an 80% power with a two-sided alpha value of 0.05.

Planned Interim Analysis and Protocol Modification

The original protocol stipulated that a single interim analysis be performed after the primary end point was evaluated in approximately 150 patients, roughly half the planned sample size of 298. However, the protocol was amended after a blinded analysis of the first sixty-six evaluated subjects indicated a higher than expected overall rate of HO ($14/66 = 21\%$) across the two treatment arms. The amended protocol stipulated a revised target of 150 randomized patients with a single interim analysis applied to the first sixty-six evaluable subjects. A nominal two-sided alpha level of 0.029 was stipulated for the interim analysis in accordance with the Pocock stopping boundary.

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Fig. 1
CONSORT flow diagram for the study.

Final Statistical Analyses

All analyses were performed in the randomized study population with use of intent-to-treat comparisons in which all subjects were analyzed in accordance with their randomized treatment assignment. The primary analysis comparing the presence of HO between the naproxen and placebo groups was performed using a Fisher exact test with a nominal two-sided alpha of 0.029 to preserve a studywise alpha level of 5% after accounting for the interim analysis. The proportions of patients experiencing adverse events at any time during the follow-up period were tabulated by randomized treatment group. All analyses were performed using SAS 9.3 software (SAS Institute).

Source of Funding

The study was funded by National Institutes of Health (NIH) Institutional Research Grant 8UL1TR000105 and the Sherman S. Coleman institutional research grant.

Results

Between August 2011 and April 2013, 108 eligible patients were enrolled and randomized. Two patients were excluded from the analysis because they did not undergo surgery,

leaving 106 patients in the study. Ten patients did not have sufficient radiographic follow-up for the final analysis of the primary measure, resulting in ninety-six patients in the final analysis. The CONSORT flow diagram for patient recruitment into the study is presented in Figure 1. Baseline patient characteristics of the groups are presented in Table I. There was a trend for a greater percentage of patients with isolated cam resection in the placebo group and a greater percentage of those with combined cam and pincer resection in the naproxen group. The data safety and monitoring board ended further enrollment into the study on the basis of our prespecified stopping criterion. The planned interim analysis indicated that HO developed in two of the thirty-two evaluable patients assigned to the naproxen group compared with twelve of the thirty-four in the control group. This resulted in a nominal p value of 0.006, which was smaller than the threshold alpha level of 0.029 for the Pocock stopping boundary, indicating that the criterion for early stopping of enrollment had been reached (Table II).

TABLE I Baseline Characteristics by Treatment Group

	Placebo (N = 54)	Naproxen (N = 52)
Female	68%	58%
Mean BMI (kg/m^2)	27.7	26.4
Mean age (yr)	35.0	35.1
Cam and/or pincer resection	94%	92%
Isolated cam resection	43%	23%
Cam and pincer resection	51%	68%
Labral repair	47%	64%
Mean no. of anchors in labral repair	1.6	2.1
Capsular closure	96%	98%
Mean no. of stitches in capsular repair	2.5	2.5
Revision for any reason	11%	9%
Revision for HO resection	4%	0%

TABLE II Development of Heterotopic Ossification at Primary Interim Analysis and Final Follow-up

	HO Prevalence		P Value
	Placebo	Naproxen	
Primary interim analysis (patients with either 3 or 6-mo radiographic assessment)*	12/34 (35%)	2/32 (6%)	0.006
Final radiographic follow-up	22/48 (46%)	2/48 (4%)	<0.001

*A nominal two-sided alpha level of 0.029 was stipulated for the interim analysis in accordance with the Pocock stopping boundary.

At the time of the interim analysis, sixty-six patients had adequate radiographic follow-up. An additional forty patients had already been enrolled over a five-month period, but they had not undergone radiographic follow-up by

the time of the interim analysis and the decision to stop enrollment.

The ninety-six patients (91% of the 106) who met the radiographic criteria to be included in the final analysis

TABLE III Frequency of Adverse Events by Treatment Group

	No. of Patients	
	Placebo	Naproxen
At least 1 adverse event	19	22
Discontinued medication early due to side effects	4	5
Gastrointestinal upset	5	7
Rash	3	1
Switched to over-the-counter NSAID for pain control	2	2
Blood clot	0	1
Heartburn	1	2
Unrelated medical condition	1	2
Weight gain	1	0
Took extra dose	1	1
Headache	1	1

underwent the final radiographic assessment at an average of 322 days, and a minimum of seventy-five days, after the index procedure. The final prevalence of HO in patients randomized to the naproxen group was 4% versus 46% in the patients randomized to the placebo group (relative risk = 0.09, exact 95% confidence interval [CI] = 0.02 to 0.38, $p < 0.001$) (Table II). All patients who developed HO had evidence of HO on three-month radiographs, substantiating our a priori decision to include patients with a minimum follow-up of seventy-five days for analysis. Two patients who developed HO postoperatively underwent revision surgery to have it resected; both patients were in the placebo group. Symptomatic HO (Brooker grade II) was the reason for the revision in one patient, whereas the primary reason for the revision surgery in the other patient was capsular laxity, not symptomatic HO (Brooker grade I).

Compliance with the study-medication protocol did not differ between the naproxen and placebo groups (69% and 68%). The two patients in the naproxen group who developed HO had complied with the medication protocol. Minor adverse reactions to the study medications were reported by 42% (twenty-two) of the fifty-two patients taking naproxen and 35% (nineteen) of the fifty-four randomized to the placebo group ($p = 0.45$). Five patients in the naproxen group and four in the placebo group stopped taking the study medication because of side effects. The reported side effects are presented in Table III. Of note, two patients in the placebo group and two in the naproxen group stopped using the study medication to use over-the-counter NSAIDs for postoperative pain control.

The morphometric characteristics and location of the HO did not differ significantly between the groups. The average two-dimensional size of the HO was 16.7 mm in the placebo group compared with 11.6 mm in the naproxen group ($p = 0.51$). In total, seventeen cases of HO were classified as Brooker grade I, and seven cases were Brooker grade II. All seven Brooker grade-II cases were observed in the control group. HO, when it occurred, always developed anterior to the hip joint.

Discussion

The primary purpose of this study was to evaluate the effect of a postoperative course of naproxen, compared with a placebo, on the development of HO after hip arthroscopy. In this trial, we found a 46% prevalence of HO in patients who did not take naproxen, a rate that was reduced to 4% (relative risk = 0.09, 95% CI = 0.02 to 0.38) when naproxen prophylaxis was used postoperatively. The prevalence of HO has been reported to be 0% to 44% without NSAID prophylaxis, compared with 0% to 8.3% with prophylaxis^{1,2,5-7}. Our findings confirm a significantly higher rate of HO in patients who do not receive NSAID prophylaxis than in those who are prescribed naproxen therapy.

Our study has several limitations. Radiographic follow-up for the primary outcome was incomplete in this study (91% [ninety-six] of 106); however, the difference that we found in the primary outcome would still be significant even if all six patients in the control group who were lost to follow-up did not develop HO and the four patients lost to follow-up in the naproxen group did develop HO ($p < 0.001$). Second, we chose

to include patients in our primary analysis who had a minimum radiographic follow-up of seventy-five days. This decision was based on our experience that HO following hip arthroscopy almost always manifests radiographically by this time point, and it is consistent with other authors' suggestion of a minimum follow-up of nine weeks (sixty-three days) for determining the presence of HO following hip arthroscopy². Although it may be possible for HO to manifest beyond seventy-five days postoperatively, that was not observed in our series.

Although there has been mounting evidence to support prophylactic NSAID therapy to reduce the risk of HO, the development of HO is multifactorial and is subject to multiple confounding variables. Temporal variations in arthroscopic procedures such as the proportion of acetabuloplasties, capsular repairs, and other surgical techniques are alternative explanations for the observed effects. We previously found that combined femoroplasty and acetabuloplasty was an independent risk factor for developing HO⁵. In the current study, the proportion of patients who underwent combined femoroplasty and acetabuloplasty was higher in the naproxen group than in the placebo group, but despite this risk factor the patients who took naproxen developed HO less frequently. Several other studies have suggested interventions to reduce the rate of HO, but because they were not randomized trials it is difficult to assess the effect of these interventions. Rath et al. postulated that capsular repair might decrease the high HO prevalence of 44% found in their study³; however, capsular repair was either not reported or was performed only following implementation of routine NSAID prophylaxis in previous studies^{2,5-7}. Less traumatic surgical techniques and greater surgical experience have been hypothesized to reduce soft-tissue trauma and curtail HO, but clinical data to support this hypothesis are limited. The present randomized study confirms that postoperative naproxen reduces the prevalence of HO following hip arthroscopy.

Previous retrospective case series have shown reductions in postoperative HO when NSAID prophylaxis was used following hip arthroscopy. Randelli et al. compared 285 patients who took NSAIDs daily for three weeks postoperatively with fifteen patients who did not take NSAIDs because of allergy or lack of compliance. Five of the fifteen patients who did not take NSAIDs developed HO, whereas none of the 285 patients who did take it showed evidence of HO formation⁷. We previously showed a thirteenfold reduction in HO formation following routine naproxen prophylaxis after hip arthroscopy in 288 patients⁵. In the present trial, we found a similar elevenfold reduction in the prevalence of HO with naproxen (4%) compared with the rate in the patients who took a placebo (46%).

NSAID therapy should not be considered benign. The potential for gastrointestinal and renal side effects with NSAID therapy, including when it is used as HO prophylaxis following hip surgery, has been well documented throughout the literature. Fransen et al. conducted a meta-analysis of 4328 patients in sixteen studies that had evaluated NSAID-related gastrointestinal side effects following total hip arthroplasty^{10,11}. Medication-related side effects were reported in 4.7% of patients taking NSAIDs for HO prophylaxis. Of these side effects,

138 were minor (e.g., nausea, dyspepsia, and diarrhea) and sixty-four were major (e.g., hematemesis or melena). Serious complications of NSAID prophylaxis have been reported following hip arthroscopy, including ototoxicity, renal failure, and hematochezia⁵. We found that minor adverse reactions to study medications were not uncommon, but the rates were similar between the naproxen and placebo groups. The high rate of minor side effects may have been decreased if we had used routine gastrointestinal prophylaxis⁶.

The clinical consequences of HO following hip arthroscopy are largely undetermined. In contrast to hip arthroplasty, for which HO prophylaxis with NSAIDs is not recommended because the risks are considered to outweigh the benefits¹¹, the consequences of HO in younger patients undergoing hip arthroscopy have been thought to justify the risks of prophylaxis. Several authors have reported performing HO resection for painful lesions. In two retrospective series, 24% and 26.5% of patients underwent resection for symptomatic anterior-based HO^{5,6}. Ong et al. found improvements in outcome scores after resection of HO in three symptomatic patients¹². These series indicate that there may be a role for HO prophylaxis because it could reduce the risk of developing symptomatic HO or requiring revision surgery for HO excision. In contrast, Rath et al. reported that the presence or absence of HO had no effect on functional outcomes as assessed with the modified Harris Hip Score and Hip Outcome Score at one year following hip arthroscopy⁷.

We confirmed that prophylactic naproxen therapy significantly reduces the prevalence of HO after hip arthroscopy. It still remains to be determined which NSAID and dosing

schedule are ideal for HO prophylaxis in this patient population. Multiple NSAIDs have been shown to reduce the prevalence of HO when given for durations as short as eight days postoperatively^{13,14}. Adding indomethacin to naproxen for HO prophylaxis has been reported to reduce the prevalence of HO compared with that after use of naproxen alone, but the use of a stronger NSAID may cause additional side effects⁶. The ideal therapy would use the lowest dose and shortest duration that still adequately reduce HO formation to minimize the side effects of routine prophylaxis. ■

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