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The Effect of Perioperative Corticosteroids in Total Hip Arthroplasty: A Prospective Double-Blind Placebo Controlled Pilot Study

Peter K. Sculco, MD [a, *], Alexander S. McLawhorn, MD [a], Natasha Desai, BA [a, b], Edwin P. Su, MD [a], Douglas E. Padgett, MD [a], Kethy Jules-Elysee, MD [b]

[a] Department of Orthopedic Surgery, Hospital for Special Surgery, New York, New York
[b] Department of Anesthesiology, Hospital for Special Surgery, New York, New York

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ABSTRACT

Background: Surgery produces a rapid rise in interleukin 6 (IL-6) which may increase the risk of deep vein thrombosis and medical complications. Perioperative corticosteroids suppress IL-6 release in patients undergoing total knee arthroplasty. This study evaluates the effects of a perioperative corticosteroid regimen on IL-6 formation, thrombogenesis, fibrinolysis, and clinical outcomes in patients undergoing unilateral, uncemented, total hip arthroplasty.

Methods: Twenty-seven patients (14 placebo and 13 study) were enrolled in this randomized, double-blind, placebo-controlled trial. The study group received 20 mg of prednisone orally followed by 2 doses of intravenous hydrocortisone, each 8 hours apart. Blood was drawn at several time points for IL-6, prothrombin fragment 1.2, and plasmin-alpha-2-antiplasmin complex, a marker of fibrinolysis. In-hospital visual analog pain (visual analog scale) scores, patient-controlled analgesia use, and ability to climb stairs were recorded.

Results: Mean serum IL-6 levels at 6 and 24 hours postoperatively were significantly lower for the study group, whereas serum prothrombin fragment 1.2 and plasmin-alpha-2-antiplasmin were not statistically different at any study time point. Average pain scores were similar ($P > .05$), but study group experience less severe pain ($P < .01$) and less patient-controlled analgesia ($P = .02$). At 3 months, 4 patients in the placebo and 1 patient in the study group had difficulty going up and down staircases ($P = .08$).

Conclusion: The use of corticosteroids was associated with a statistically significant decrease in IL-6 at 6 and 24 hours postoperatively but did not affect thrombogenic markers. The study group had improved postoperative analgesia and a trend toward improved functional outcome at 3 months postoperatively.

The administration of perioperative corticosteroids in patients undergoing bilateral and unilateral total knee arthroplasty (TKA) has been shown to reduce the postoperative rise of serum markers for systemic inflammation, lung injury, and the coagulation cascade [1,2]. Prothrombin fragment 1.2 (PF1.2), a serum marker for thrombogenesis, and plasmin-alpha-2-antiplasmin (PAP), a serum marker for fibrinolysis, are useful for the detection of hypercoagulable states characterized by the risk of thrombosis [3]. PF1.2 increases sharply only after tourniquet release in TKA [4]. In contrast, PF1.2 increases rapidly after the surgical incision in total hip arthroplasty (THA) suggesting that wound blood has immediate effects on the coagulation cascade [5]. In patients undergoing primary TKA, perioperative corticosteroids were found to decrease serum PF1.2 and were associated with a significant reduction in IL-6 [1]. Other short-term clinical benefits included a lower incidence of postoperative fever, lower visual analog pain scores, and improved knee motion without any increase in complications [6]. To our knowledge, no study has examined the effect of perioperative corticosteroids on the inflammatory marker IL-6 and prothrombotic and fibrinolytic markers, PF1.2 and PAP, in patients undergoing primary THA. In addition, it is not known whether perioperative corticosteroids will produce similar clinical benefits as found in bilateral TKA patients.

The purpose of this study was to compare the mean difference in perioperative serum concentrations of IL-6, PF1.2, and PAP after

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* Reprint requests: Peter K. Sculco, MD, Department of Orthopedic Surgery, Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021.

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THA between 2 randomized groups: one receiving systemic corticosteroids and the other receiving a placebo. The principal study hypothesis was that perioperative administration of systemic corticosteroids would significantly decrease the postoperative rise in PF1.2 levels. Furthermore, it was hypothesized that the perioperative administration of systemic corticosteroids would reduce systemic IL-6 and increase systemic PAP. The secondary aims of this study were to evaluate whether patients receiving systemic corticosteroids will experience less perioperative pain and exhibit improved pain and functional outcomes at 3-months postoperatively.

Materials and Methods

After approval from the hospital Institutional Review Board, a total of 40 patients enrolled in this prospective, double-blinded, placebo-controlled randomized trial. The study was registered at www.ClinicalTrials.gov (number: NCT01782859). All subjects gave their written informed consent for participation in the study before surgery. The research was conducted between October 2012 and April 2014, at a single, urban, specialty hospital.

Adult patients undergoing primary, unilateral, uncemented THA through the posterior approach were eligible for inclusion. Exclusion criteria included diabetes mellitus, current steroid therapy, smoking history, prior history of corticosteroid intolerance, and previous complications related to steroid use. Patients on nonsteroidal anti-inflammatory drugs or aspirin before surgery held the medications 1 week preoperatively.

Patients were divided into 2 groups. The experimental group received 20 mg of prednisone orally (oral equivalent of 100-mg intravenous hydrocortisone) 2 hours preoperatively, followed by 2 doses of 100-mg intravenous hydrocortisone sodium succinate, each 8 hours apart. The control group received a placebo at the same time points. Study medications were prepared by the hospital pharmacy. Three surgeons performed all operations with standard surgical technique using the posterior approach and uncemented acetabular and femoral implants. All patients received an arterial line and spinal/epidural anesthesia. Postoperatively, analgesia consisted of epidural patient-controlled analgesia (PCA). PCA dosing consisted of bupivacaine and hydromorphone with total administered volume recorded daily by a blinded medical provider. Other nonsteroidal anti-inflammatory agents were not used. The deep drain was removed on postoperative day 1. The epidural catheter was removed on postoperative day 1 at 12:00 PM. Aspirin therapy was initiated the night of surgery for venous thromboembolism (VTE) prophylaxis and was continued for 6 weeks postoperatively (goal international normalized ratio: 1.8-2.2).

The primary outcome was the serum concentration of the thrombogenic marker, PF1.2. Secondary outcome measures included serum PAP, IL-6, and glucose; in-hospital VAS (daily means and maxima); total PCA volume; hospital length of stay; patient-reported nausea, emesis, and pruritus on each postoperative day; visual analog scale (VAS) assessment; and patient-reported difficulty rising from a seated position, negotiating stairs, sitting, and walking at 3-months postoperatively. Blood was drawn at baseline, wound closure, 4 hours, 6 hours, and 24-hours postoperatively for assays of serum IL-6, PF1.2, and PAP. Serum glucose was recorded daily through the second postoperative day.

An a priori power analysis using published data was performed [4]. It was determined that a sample size of 10 patients in each study would confer 80% power with 5% type I error to detect a 25% reduction in the mean PF1.2 level at any time point postoperatively.

Patients were enrolled at their presurgical hospital visit, several days before their elective THA. Randomization was performed at the time of enrollment. Patient allocation to either the study or the control group was done by utilization of a randomization table prepared by the hospital pharmacy. Group allocations were concealed before enrollment. All study personnel involved, except pharmacy, were blinded to the randomization process. See Figure 1 for the CONSORT patient flow diagram.

Statistical Analysis

Continuous and discrete variables were presented as mean ± standard deviation and frequencies (%), respectively. Two independent-sample *t* tests were used to compare continuous variables, and Fisher's exact test was conducted to compare discrete variables. All analyses were performed using SPSS 13.0 for Windows (Chicago, IL) and SAS 9.1 for Widows (Cary, NC). A critical *P* value of .05 was used for all hypothesis tests.

Results

A total of 27 patients (14 control patients and 13 study patients) were analyzed for this trial. Three patients in the control group and 4 patients in the study group were excluded from analysis because of various protocol deviations (Fig. 1). Baseline demographic characteristics were similar in both groups (Table 1). Serum PF1.2 and PAP levels were not significantly different between study groups at any time point (Table 2). Mean IL-6 levels showed no difference between groups at baseline, wound closure, or 4 hours postoperatively. However, significantly reduced mean IL-6 concentrations were noted in the study group at 6 and 24 hours postoperatively compared to the control group (See Fig. 2.) In both groups, PF1.2 and PAP levels approached baseline at 24 hours postoperatively (Table 2). The highest mean level for both PF1.2 and PAP in the control and study groups was 4 hours postoperatively. The time course of these coagulation markers reflects activation of the coagulation cascade followed by a decline in thrombogenic and fibrinolytic markers at 24 hours postoperatively. In contrast, IL-6 levels remained significantly elevated in the control group compared to the study group and were significantly different at 6 and 24 hours postoperatively ($P < .01$).

Mean postoperative serum glucose was significantly elevated in the study group on the day of surgery, but differences between groups abated on the subsequent postoperative days (Table 3). Mean postoperative VASs were not significantly different between groups (Table 3). However, mean peak postoperative VASs were significantly less in the study group on the day of surgery and the second postoperative day. Furthermore, total administered PCA medication volume was significantly less in the study group compared to the control group (101.0 ± 42.5 vs 140.1 ± 44.3 mL, $P = .02$). There was no intergroup difference in the frequency of patient-reported nausea, emesis, and pruritus at any study time point. Length of stay was 76.56 ± 26.34 hours for the control group and 83.61 ± 22.17 hours for the study group ($P = .46$).

Clinical outcomes at 3 months postoperatively demonstrated a trend toward improved stair climbing in the study group with only 1 patient (7.6%) having difficulty with stairs vs 4 patients (28.57%) in the control group ($P = .08$; Table 4). There were no statistically significant intergroup differences in other subjective functional assessments and mean VAS at 3 months after THA surgery.

There were no wound complications, deep infections, or clinically apparent VTE in either group during the study period.

Discussion

In this prospective, randomized, double-blind, placebo-controlled pilot study of patients undergoing unilateral primary THA, perioperative corticosteroid administration significantly