Single-Dose Dexamethasone Reduces Dynamic Pain After Total Hip Arthroplasty

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BACKGROUND: Preoperative glucocorticoids reduce postoperative nausea but may also improve analgesia and decrease opioid consumption.

METHODS: Fifty consecutive patients undergoing elective, unilateral, primary total hip arthroplasty under spinal anesthesia with propofol sedation received in a randomized, double-blind, placebo-controlled manner either 40 mg of dexamethasone or saline placebo IV before the start of surgery. IV patient-controlled analgesia morphine, ibuprofen 400 mg po q6 h and acetaminophen 650 mg po q6 h were given for 48 h. Pain (0–10 numeric rating scale, NRS) at rest, side effects, and total cumulative patient-controlled analgesia morphine consumption were recorded q4 h for 48 h. Dynamic pain NRS score was recorded at 24 h. C-reactive protein levels were measured in a subgroup of 25 patients at 48 h.

RESULTS: The intraoperative sedation requirement with propofol was significantly increased in the dexamethasone group (234.6 ± 160.1 vs 138.8 ± 122.7 mg, $P = 0.02$). Dynamic pain was greatly reduced in the dexamethasone group (NRS score: 2.7, 95% CI: 2.2–3.1 vs 6.8, 6.4–7.2; $P < 0.0001$). There was no significant effect on pain at rest or cumulative morphine consumption at any time. C-reactive protein levels at 48 h were markedly reduced by dexamethasone (52.4 mg/mL, 28.2–76.6 vs 194.2, 168.9–219.4; $P < 0.0001$). Seven patients in the control group, but only one in the dexamethasone group, were treated for nausea ($P = 0.05$).

CONCLUSIONS: A single, preoperative IV dose of dexamethasone 40 mg has a prolonged suppressive effect on the inflammatory response and decreases dynamic pain 24 h after total hip arthroplasty.

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Dexamethasone is a high-potency, long-acting glucocorticoid with little mineralocorticoid effect that has been extensively used in the perioperative setting.[1,2] A single preoperative dose of dexamethasone has gained widespread acceptance as an effective preventive treatment of postoperative nausea.[3] The minimally effective dose for this effect seems to be <8 mg in adults.[4,5] No increase in antiemetic effect was observed beyond 0.0625 mg/kg after pediatric tonsillectomy.[6] Recently, single doses of larger amounts of dexamethasone and other glucocorticoids have also been reported to improve analgesia after various operations, including foot,[7] breast,[8] laparoscopic cholecystectomy,[9] and spine surgery.[10,11] One study found that a single dose of methylprednisolone 125 mg given the day after lower limb orthopedic surgery had sustained analgesic, opioid-sparing, and antiemetic effects over a 3-day period.[12]

Total hip arthroplasty (THA) is an increasingly common operation that results in significant postoperative pain. At our institution, postoperative analgesia for THA is provided by IV patient-controlled analgesia (PCA) with morphine and regular oral doses of acetaminophen and ibuprofen. Patients are often distressed by nausea and other opioid side effects from this regime. Epidural and continuous femoral nerve block analgesia have been shown to reduce opioid use in this setting compared with PCA,[13] but both modalities involve extra equipment and the potential risk of neurological sequelae.[14] The prospect of improving multimodal analgesia after major orthopedic surgery while reducing side effects with a single preoperative administration of steroid is enticing.[15]

C-reactive protein (CRP) is an acute phase plasma protein that serves as a marker of inflammation. In a study of the neuroendocrine and inflammatory responses after THA, CRP levels were found to peak at 48 h.[16] The magnitude of this increase in CRP was found to correlate with pain and functional outcome in the postoperative period until hospital discharge. It has been suggested that this postoperative inflammatory response may be more effectively inhibited by systemic glucocorticoids than regional anesthesia.[16]

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The hypothesis of this randomized, controlled trial was that a single, preoperative IV dose of dexamethasone 40 mg would reduce dynamic pain 24 h after THA due to its prolonged antiinflammatory effect. Secondary outcomes included pain at rest, opioid use, and side effects, as well as CRP levels at 48 h.

METHODS

With IRB approval and informed written consent, 50 patients undergoing elective, unilateral, primary THA under spinal anesthesia were enlisted in this double-blind, randomized, placebo-controlled, parallel study.

Patients were enlisted on the day of surgery and were randomly assigned to receive either 40 mg of IV dexamethasone or saline placebo.

Exclusion criteria were age <18, inability to communicate lucidly in English or French, revision hip replacement, contraindication to spinal anesthesia (back fusion, coagulopathy, local infection), renal failure, peptic ulcer disease, treatment with steroids or immunosuppressive drugs in the last 6 mo, diabetes mellitus type I or II, and hypersensitivity to bupivacaine, morphine, nonsteroidal antiinflammatories (NSAIDs), or the study drug.

Randomization and Blinding Methods

Eligible patients were block randomized using a computerized random number generator with 25 patients allocated to each group. A collaborator not involved in data collection prepared and dispensed dexamethasone 40 mg (4 mg/mL, Sabex, Boucherville, Canada) or equal volume of saline added to 40 mL of normal saline in an IV infusion bag according to the randomization list. Dexamethasone is colorless in solution and painless on injection. The patient, anesthesiologist, or observers collecting data were unaware of the patient's study group allocation.

Anesthesia and Postoperative Pain Management

Preoperatively, normal saline infusion via an 18-gauge IV was started. Sedation with an IV propofol infusion was administered at the discretion of the anesthesiologist, and the total dose throughout the case recorded. Spinal anesthesia was induced in the sitting position at the L2–3 level using a 25-gauge Whitacre spinal needle (Becton-Dickinson, Franklin Lakes, USA) with a dose of 15 mg plain 0.5% bupivacaine (Hospira, Montreal, Canada) and patients immediately laid supine. After onset of anesthesia to light touch over the greater trochanter on the operative side, the study drug or placebo control was administered IV over 10 min. No opioids were given intraoperatively. Total surgical time was recorded as the interval between skin incision and arrival in recovery room.

Postoperatively, PCA with morphine was used. Initial doses of morphine 1–2 mg IV q5 min were given when the patient first complained of any pain, to achieve a rating of <4 on a scale of 0–10. Subsequently, 1 mg IV q7 min prn was used for 48 h. All patients also received acetaminophen 650 mg po q6 h and ibuprofen 400 mg po q6 h, with the first dose administered when PCA morphine was started. Time to first PCA dose was measured from arrival in the recovery room.

Assessment and Data Collection

Hip pain was measured both at rest and as dynamic (standing up) scores on an 11-point numeric rating scale (NRS score: 0 = no pain, 10 = worst pain imaginable). Baseline preoperative values were recorded by the anesthesiologist for each case. Postoperative pain scores at rest were collected by recovery room and then ward nurses every 4 h for 48 h. Dynamic pain scores were recorded at 24 h by a single physiotherapist, before physiotherapy began, using the same 11-point NRS. Total time in the recovery room for discharge criteria to be met (full restoration of bilateral leg sensation and movement, resting pain NRS score < 4, as assessed by nurses) was noted.

Side effects were assessed by recovery room and ward nurses q4 h during the 48 h study period, at the same time as rest pain assessments. Level of sedation on a 5-point NRS (1 = fully alert, 5 = arousable only with painful stimulation) was noted. Nausea and pruritus were defined as episodes requiring treatment standardized in our PCA protocol (prochlorperazine 10 mg IV or diphenhydramine 50 mg IV, respectively). Urinary retention requiring catheterization, based on bladder ultrasound showing more than 500-mL volume, was recorded.

CRP levels were measured at 48 h on the last 25 patients randomized. Assays were done on venous blood samples by turbidimetric technique on a Hitachi Cobas 800 analyzer.

One month after surgery, each patient's inpatient and outpatient follow-up hospital record was reviewed by the same investigator (F.S.) for any documentation of wound complications or infection.

Power Analysis

This calculation was based on the results of a previous study involving lower extremity orthopedic surgery.[12] Their placebo group patients had a baseline rest pain score at 24 h of approximately 7/10, with a standard deviation of approximately 2. This was similar to dynamic pain levels we had observed in our patient population in pilot observations. Setting the statistical power of 80%, α for statistical significance at 0.05 (two-sided test), the mean 7, and increasing the standard deviation to 2.5 to be conservative, a sample size of 23 subjects for each group is sufficient to detect a 30% decrease in pain score (or 2.1 NRS). We chose a group size of 25 to allow for possible dropouts. Sample size calculation was performed with Power and Sample Size Calculation (version 1.0.15).

Table 1. Demographic and Intraoperative Data

Variable	Placebo ($N = 25$)	Dexamethasone ($N = 25$)	P
Age (yr)	68.8 ± 11.4	69.0 ± 7.2	NS
Gender (F/M)	14/11	12/13	NS
Weight (kg)	74.2 ± 15.3	76.9 ± 11.6	NS
Height (cm)	166.9 ± 10.2	168.0 ± 8.9	NS
Total propofol dose (mg)	138.8 ± 122.7	234.6 ± 160.1	0.02
Drug injection to incision (min)	21.8 ± 6.5	19.8 ± 3.5	NS
Surgery duration (min)	119.8 ± 29.7	103.24 ± 22.0	0.03

Data presented as mean ± SD. Two-tailed P for χ^2 and unpaired t statistics. Drug injection to surgical incision interval measured from beginning of study drug infusion.

NS = not statistically significant with [*alpha*] of $P < 0.05$.

Table 2. Pain at Rest (0–10 NRS)

	Mean NRS (0–10)	
Time after surgery (h)	Placebo ($N = 25$)	Dexamethasone ($N = 25$)
Baseline	1.0 ± 1.6	1.0 ± 1.6
4	2.5± 2.0	2.1 ± 2.1
8	3.4 ± 2.4	2.3 ± 1.9
12	3.1 ± 2.1	2.4 ± 1.7
16	2.6 ± 1.9	2.0 ± 1.4
20	2.2 ± 1.9	1.9 ± 1.6
24	1.9 ± 1.8	1.5 ± 1.1
28	1.5 ± 1.4	1.6 ± 1.6
32	1.3 ± 1.2	1.3 ± 1.3
36	0.9 ± .8	0.9 ± 1.1
40	0.9 ± 1.0	0.8 ± 1.1
44	0.6 ± .8	0.6 ± 1.0
48	0.3 ± .6	0.3 ± .5

Data presented as mean ± SD. Two-tailed P for unpaired t statistics. No significant difference between groups.

NRS = numerical rating scale.

Statistical Analysis

Baseline data were compared between groups using one-way ANOVA for continuous measures and Pearson's χ^2 for categorical measures. Descriptive results are reported as mean and standard deviation (±SD). All continuous outcomes were compared between groups using Proc GLM general linear analyses. Analyses were on an intention-to-treat basis and adjusted by the baseline differences between groups (Table 1). These results are reported as mean and 95% confidence intervals (95% CI). Fisher's exact test was applied to assess the difference between groups related to side effects. Secondary analysis was performed by repeated-measures analyses (linear mixed model, PROC MIXED, SAS) to account for the correlation between the levels of rest pain across different times during the study. We chose the best model based on Akaike's Information Criterion. The level of significance was 0.05 (two-sided) in all statistical tests. There was only one missing data point, for total morphine use at 16 h in one patient. This data point was replaced by the average of the mean values observed at 12 and 20 h. Statistical analyses were performed using SAS software version 9.1.

Table 3. Cumulative Morphine Consumption

	PCA morphine consumption (mg)	
Time after surgery (h)	Placebo ($N = 25$)	Dexamethasone ($N = 25$)
4	4.3 ± 3.5	4.3±4.8
8	9.8 ± 5.1	9.6 ± 8.2
12	15.4 ± 8.6	13.3 ± 10.5
16	19.6 ± 11.9	16.9 ± 11.2
20	24.6 ± 15.0	18.9 ± 11.5
24	28.8 ± 16.5	21.6 ± 11.8
28	31.3 ± 17.9	23.7 ± 12.7
32	34.3 ± 18.9	26.1 ± 14.5
36	37.1 ± 19.8	29.1 ± 15.3
40	39.9 ± 20.7	30.5 ± 15.9
44	41.7 ± 21.4	31.8 ± 16.9
48	42.9 ± 21.7	32.8 ± 17.5

Data are presented as mean ± SD. Two-tailed P for unpaired t statistics. No significant difference between groups.

PCA = patient-controlled analgesia.

Table 4. Side Effects

Variable	Placebo $N = 25$	Dexamethasone $N = 25$
Urinary retention	0	3
Nausea requiring treatment	7	1
Pruritus requiring treatment	1	2
Sedation score >1	4	5

Data represent cumulative number of patients over 48 h. Two-tailed P for Fisher's exact test. No significant difference between groups.

RESULTS

Sixty-seven patients were approached to participate. Fifteen were ineligible for the study because of chronic opioid use ($n = 7$), recent steroid use ($n = 4$), intolerance to study medications ($n = 3$), and communication difficulty ($n = 1$). Of the 52 eligible, all consented to participate. Two patients were excluded from study because of failure to achieve spinal anesthesia. Among the 50 patients randomized to the study, there were no significant differences between groups in demographic variables. Surgical time was shorter, and intraoperative propofol use was greater, in the dexamethasone group (Table 1). The results are reported as mean (±SD).

There was no significant difference in pain at rest NRS scores at any time period (Table 2).

Dynamic pain NRS score at 24 h was, however, much lower in the dexamethasone than in placebo group (2.6, 95% CI: 2.2–3.0 vs 6.9, 95% CI: 6.5–7.3, respectively; $P < 0.0001$). This significant effect remained in an adjusted analysis (2.7, 95% CI: 2.2–3.1 vs 6.8, 95% CI: 6.4–7.2; $P < 0.0001$), considering surgical time and intraoperative propofol use.

Mean cumulative PCA morphine consumption was lower in the dexamethasone group at each time period

measured, and total 48 h use was reduced by 23%, but these results were not statistically significant (Table 3).

There was no difference between groups in time to first dose of PCA morphine after surgery (67 min, 95% CI: 41.7–92.3 vs 98 min, 95% CI: 72.7–123.3, dexamethasone versus placebo, $P = 0.09$) and total time in recovery room (210 min, 95% CI: 185.0–234.6, vs 198 min, 95% CI: 173.2–222.9, $P = 0.50$).

CRP levels were measured at 48 h in 13 patients in the dexamethasone group and 12 in the placebo group. There were no significant differences in demographic and intraoperative variables between treatment groups in this sample subset. CRP levels were significantly lower in the dexamethasone group (46.6 mg/L, 95% CI: 20.3–73.0 vs 200.4 mg/L, 95% CI: 173.0–227.8, $P < 0.0001$). The difference remained significant after multivariate analysis (52.4 mg/L, 95% CI: 28.2–76.6 vs 194.2 mg/mL, 95% CI: 168.9–219.4; $P < 0.0001$). The normal range for CRP assay at our institution is 0–10 mg/L.

All treatments for nausea occurred in the first 24 h. There were seven patients treated in the placebo group and only 1 in the dexamethasone group ($P = 0.05$). There was no difference in the incidence of urinary retention, pruritis, or sedation over the 48-h observation period (Table 4). The maximum sedation score recorded was 2. At 1 mo postoperatively, no wound complications or infections had been reported in any patient in either group.

DISCUSSION

The most clinically significant result of our study was the marked reduction in pain with movement (standing) at 24 h in patients receiving dexamethasone. The high dynamic pain scores in the control group highlight the relative ineffectiveness of opioid-NSAID analgesia in controlling this type of pain. Despite the robust, almost three-fold difference in this variable it is true that it is an isolated finding. Unfortunately, the physiotherapist's assessment was only available at 24 h postoperatively. The dramatic decrease in CRP levels at 48 h, however, supports our hypothesis that single-dose dexamethasone can be expected to have measurable antiinflammatory effects for at least 48 h. We did not collect range of motion data, but it would be interesting to assess the impact of such dramatic decreases in pain on functional outcomes.

The lack of any significant difference in pain at rest between groups at any time point may reflect the effective multimodal analgesia received by all patients: mean NRS score (0–10) peaked at 3.4 in the placebo group at 8 h postoperatively; both groups had mean scores consistently below 2 beyond 24 h. This may also explain why, unlike Romundstad et al.'s results after lower limb orthopedic surgery,[12] we could not demonstrate a clearly significant difference in 48-h opioid consumption despite having the same treatment group size. In their study, patients did not receive regular doses of NSAIDs.[12]

Despite a seven-fold difference in incidence between groups, we could not demonstrate a clearly significant antiemetic effect of dexamethasone ($P = 0.05$). This was surprising in view of the extensive literature supporting its efficacy after general anesthesia.[3] This may simply reflect our study being insufficiently powered to demonstrate a difference. Another possible explanation may relate to the fact that our patients underwent spinal anesthesia. Also no effect on nausea was noted in the lower limb surgery trial using methylprednisolone.[12] In that series, most patients received spinal anesthesia and the study drug was not given until 24 h after surgery.

The dose of dexamethasone we used was much larger than the minimally effective IV dose for prevention of postoperative nausea.[3–6] Dexamethasone 8 mg given 90 min preoperatively decreased pain and analgesic requirements after laparoscopic cholecystectomy.[9] However, 8 mg had no effect on postoperative analgesia when given IV for major orthopedic surgery.[17] Methylprednisolone 125 mg was shown to improve analgesia after lower limb orthopedic surgery.[12] Based on a theoretical 5:1 glucocorticoid potency ratio,[1,2] this would be equivalent to 25 mg of dexamethasone. We chose 40 mg based on reports of analgesia after spine surgery with this dose.[10,11]We wanted to test a systemic dose of dexamethasone that had been empirically demonstrated as having analgesic efficacy in major orthopedic surgery. Dose-finding studies are required to identify the minimally effective dose for this effect relative to nausea prophylaxis.

Administering the dexamethasone as a diluted infusion over at least 5 min was an important methodological point. If given too rapidly, even in doses as small as 8 mg, dexamethasone causes a perineal flushing reaction, particularly in female patients, that can be distressing. This may be related to the phosphate buffer rather than the drug itself.[18,19]

An unexpected finding was the significantly larger amounts of propofol sedation used in the dexamethasone group. This was despite a statistically, if not clinically, significantly shorter (by 17 min) duration of surgery. The difference in propofol use remained significant after multivariate analysis adjusted for surgery duration. Dexamethasone may have increased sedation requirements through its central nervous system-stimulating side effects. Insomnia and agitation are described as characteristic side effects of dexamethasone when used in the setting of postchemotherapy nausea prophylaxis.[20] However, no signs of agitation were observed in any patient in our series, and there was no difference in sedation scores between the groups postoperatively. It may also be that this is a spurious result due to the lack of a standardized administration regimen for propofol in our study.

Despite the documented safety of the widespread use of dexamethasone for nausea prophylaxis,[21] it is possible that larger doses may increase the risk of side effects seen with chronic use. The most important potential risks in the postoperative period would be gastrointestinal bleeding,[22] impaired wound healing,[23] or increased susceptibility to infection.[24] A particularly rare and insidious complication that has been associated with chronic glucocorticoid use is avascular necrosis of the femoral head. Symptoms may present months, or even years, after steroid administration.[25] In a meta-analysis of 51 studies including more than 1900 patients receiving doses of 15–30 mg/kg methylprednisolone (equivalent to approximately 10 times our dose), no significant increase in risk of any of these side effects was found.[26] Many of these studies were conducted in settings at even higher risk for complications than elective THA, such as cardiac, spine, and trauma surgery. In fact, the only significant effect on morbidity observed was a reduction in pulmonary complications, noted particularly in patients with fractures. In reviewing the literature, we were unable to find any clinical studies demonstrating a significant increase in incidence of serious adverse effects after single-dose glucocorticoid administration at any dose. This absence of proof does not prove absence of risk, however. A limitation of our and other studies of single-dose steroid use is the lack of both strict follow-up methodology and statistical power to meaningfully assess the incidence of uncommon adverse effects. We can only caution that careful risk-benefit consideration be given to the use of any glucocorticoid for postoperative analgesia. This may include considering a gastroprotective regimen, particularly if given in combination with NSAIDs.[11] Future studies to determine the minimum effective dose for analgesia would be of interest.

In conclusion, a single, preoperative dose of dexamethasone 40 mg IV resulted in less dynamic pain at 24 h and lower CRP levels at 48 h after THA. Further data to define the benefits and potential adverse effects of this approach to multimodal analgesia are needed.

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