The Journal of Arthroplasty xxx (2019) 1–7

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

# Intravenous Dexamethasone Injection Reduces Pain From 12 to 21 Hours After Total Knee Arthroplasty: A Double-Blind, Randomized, Placebo-Controlled Trial

Nattapol Tammachote, MD, MSc *, Supakit Kanitnate, MD

*Department of Orthopaedics, Faculty of Medicine, Thammasat University, Khlong Luang, Pathumthani, Thailand*

ARTICLE INFO

*Article history:*
Received 24 June 2019
Received in revised form
7 August 2019
Accepted 2 September 2019
Available online xxx

*Keywords:*
dexamethasone
corticosteroid
pain control
total knee arthroplasty
nausea and vomiting
C-reactive protein

ABSTRACT

*Background:* Pain after total knee arthroplasty (TKA) affects postoperative recovery and patient satisfaction. The analgesic benefits of corticosteroids have not been well studied. We, therefore, investigated the analgesic effects of intravenous (IV) dexamethasone (DEX) in patients undergoing a TKA.
*Methods:* This was a randomized, double-blind, placebo-controlled trial of 0.15 mg/kg of IV DEX vs saline placebo in unilateral TKA. Fifty patients/arm were recruited. Primary outcomes were pain level, determined by a visual analog scale, and the amount of morphine consumption (mg) ≤48 hours post-TKA. Secondary outcomes were rates of nausea and vomiting, C-reactive protein concentrations, and functional outcomes.
*Results:* The DEX group had a significantly lower mean visual analog scale score both at rest and during motion at 12, 15, 18, and 21 hours ($P < .05$). At 21 hours, the mean difference (Δ) in pain at rest was −11 points (95% confidence interval [CI], −21 to −2 points; $P = .02$) while the mean difference in pain during motion was −15 points (95% CI, −25 to −5 points; $P = .004$). The DEX group also had lower rates of nausea and vomiting: 29/50 (58%) vs 42/50 (84%) ($P = .008$) and lower mean C-reactive protein level: 89 vs 167, Δ = −78 mg/L (95% CI, −100 to −58 mg/L, $P < .0001$). There were no significant differences in mean morphine consumption by 48 hours, modified Western Ontario and McMaster University Osteoarthritis Index scores, and range of motion of the knee at 3-month follow-up ($P > .05$).
*Conclusion:* IV DEX relieves postoperative pain between 12 to 21 hours after TKA and may be a useful adjunct for controlling pain in patients undergoing TKA.



Acute postoperative pain after total knee arthroplasty (TKA) affects patient functional recovery and satisfaction [1]. Multimodal analgesic drugs have been proposed to optimally control pain and include opioids, nonsteroidal anti-inflammatory drugs, acetaminophen, and gabapentinoids. Sometimes the use of multimodal drugs may be contraindicated, for example, nonsteroidal anti-inflammatory drugs in patients with chronic kidney disease.

Dexamethasone (DEX) is a long-acting glucocorticoid, which has powerful anti-inflammatory properties and some mineralocorticoid effects. It inhibits peripheral phospholipase resulting in a decrease of pain-activated products from the cyclooxygenase and lipoxygenase pathways [2]. It has frequently been administered in the preoperative period to reduce postoperative nausea and vomiting (PONV) [3]. A meta-analysis of randomized controlled trials (RCT) of intravenous (IV) DEX, dosed at >0.1 mg/kg, suggested it was an effective adjunct to reduce pain and had opioid-sparing effects after surgery [4]. Unfortunately, this meta-analysis included many kinds of surgery but only 1 study focused on total hip arthroplasty. Several types of IV corticosteroids have been prescribed to control pain after TKA including DEX [5,6], methylprednisolone [7], and hydrocortisone [8,9]. DEX had less fluid retention compared to the other corticosteroids due to its lower mineralocorticoid effect. There has not been a high-quality, randomized, placebo-controlled trial that has examined the effect of IV DEX in controlling pain after TKA.

The purpose of this study is to systematically evaluate the analgesic efficacy of single-dose preoperative IV DEX compared with placebo in patients undergoing unilateral primary TKA.

Investigation was performed at the Orthopedic unit, Thammasat University Hospital, Thammasat University, Pathumthani, Thailand.

No author associated with this paper has disclosed any potential or pertinent conflicts which may be perceived to have impending conflict with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2019.09.002.

* Reprint requests: Nattapol Tammachote, MD, MSc, Department of Orthopaedics, Thammasat University, 99 Moo 18, Khlong Nueng, Khlong Luang, Pathumthani, 12120, Thailand.

https://doi.org/10.1016/j.arth.2019.09.002
0883-5403/

## Materials and Methods

This was a single-center, double-blind RCT with 2 parallel groups comparing the efficacy of IV DEX with placebo in controlling pain after TKA. The study was conducted from May 2014 to June 2016 at Thammasat University Hospital, a tertiary referral hospital. The ethical review board approved this study (MTU-EC-OT-1-126/56), and it was registered at www.clinicaltrials.gov (NCT02102815). All patients provided written informed consent and agreed to participate in this trial.

### *Participants*

The inclusion criteria were the following: (1) patients with osteoarthritis of the knee who underwent unilateral TKA, (2) age between 50 and 85 years, (3) American Society of Anesthesiologists physical status class I-III, (4) accomplished spinal anesthesia, and (5) gave informed consent to participate in this study. The exclusion criteria included: (1) cognitive functional impairment, (2) severe kidney or liver disease, (3) allergy to any of the study drugs, (4) poorly controlled diabetes mellitus (HbA1C > 7.5%), and (5) received systemic corticosteroids within 3 months before surgery.

### *Randomization*

A research assistant, not otherwise involved in the trial, generated the randomization list in blocks of 4. The allocation sequences (1:1 allocation rate) were concealed in 100 consecutively numbered, opaque, sealed envelopes, which were opened by study nurses after successful spinal anesthesia (levels L3-L4 or L4-L5 using 27-gauge spinal needle with 10-15 mg of 0.5% bupivacaine). The patients were given either IV DEX (DEX group) or IV saline (placebo group). An anesthetist nurse, who was not involved with patient data collection, prepared and administered the DEX or saline before surgery started.

### *Study Interventions and Drug Protocol*

The DEX group received a 1-time dose of 0.15 mg/kg (4 mg/mL) of dexamethasone phosphate (LODEXA, L.B.S. Laboratory Ltd, Bangkok, Thailand) diluted with normal saline to 50 mL; the maximum dose of DEX in this study was 12 mg. The drug was slowly injected over 5 minutes to reduce perineal pruritus and pain [10]. The placebo group received 50 mL of isotonic saline. Patients, surgeon, and the evaluator (S. Kanitnate) were blinded to the treatment allocation throughout the study. The anesthetist nurse who prepared and gave the drug injections was not involved in patient assessment.

All surgeries were done by or under the supervision of 1 surgeon (N. Tammachote) using a standard medial parapatellar arthrotomy. We used a pneumonic tourniquet with pressure equal to the patient's systolic blood pressure plus 120 mmHg before the skin incision and released it after wound closure. Also, 750 mg of IV tranexamic acid was injected before the skin closure. Suction drains were not used. The multimodal periarticular drug injection was injected in all patients, consisting of 100 mg of 5% bupivacaine (20 mL), 30 mg of ketorolac (1 mL), 5 mg of morphine sulfate (5 mL), 0.6 mg of epinephrine (0.6 mL), mixed with saline until total volume equal to 100 mL.

All patients received the same postoperative pain control protocol. In the first 48 hours after surgery, we administered 15 or 30 mg of ketorolac IV every 6 hours, adjusted for age and kidney function (if the age was more than 65 years or the creatinine clearance was less than 50 mL/min, patients would receive 15 mg of ketorolac). Three milligrams of IV morphine was given as patient needed every 3 hours. On the third postoperative day, 250 mg of oral naproxen was administered twice daily after meals and 50 mg of tramadol was administered only when patients requested it, up to every 6 h. We also gave 1300 mg of extended-released acetaminophen every 8 h, and 25 mg of nortriptyline together with 75 mg of pregabalin at bedtime. Patients were encouraged to do foot pump exercise and started to walk with a walker on the second day after surgery. All patients were followed up at 2, 6, and 12 weeks after surgery.

### *Study Assessments*

The primary outcomes were pain level and the amount of morphine consumption. The pain level was measured every 3 hours until 48 hours after surgery and was recorded by patients themselves using a 100-mm visual analog pain scale (VAS) at rest and during motion (knee flexion >45°). A 0 mm indicated no pain while 100 mm indicated extreme pain in 1-mm increments. The amount of morphine consumption was recorded every 12 hours until 48 hours after surgery.

The secondary outcomes were the following: (1) rate of PONV, (2) CRP levels (baseline and 48 hours), (3) functional outcomes, and (4) steroid complications. PONV was defined as any feeling of nausea, retching, or vomiting occurring during 24-48 hours after surgery. The patients recorded these symptoms by themselves in the first 48 hours after surgery. Functional outcomes were measured using the modified Western Ontario and McMaster University Osteoarthritis Index (WOMAC) [11] and knee range of motion (ROM) includes knee flexion and extension angle preoperatively, and at weeks 6 and 12 after surgery. Adverse effects of DEX were assessed by blood glucose concentrations and wound infection rates; glucose was measured in the morning before surgery and at 24 and 48 hours after surgery. Wounds were assessed until 12 weeks after operation. The investigator (S. Kanitnate) who was not aware of the patient's allocation collected all data in this study.

### *Statistical Analysis*

The sample size was calculated to detect a mean difference of 12 points in the VAS score between the 2 groups. The mean and standard deviation VAS scores at 24 hours postoperatively in patients who received IV steroid were approximately 40 and 20 points, respectively [7]. For a 2-sided alpha of 0.05 and power of 80%, the calculated sample was 50 patients per arm (including 10% dropouts).

The Student *t*-test was used to estimate the mean differences in VAS at rest and during motion, the amount of morphine consumption, and levels of CRP. The frequencies of PONV and wound complications were analyzed using the 2-tailed Fisher exact test. Repeated measures analysis of variance was used for comparing modified WOMAC and ROM between groups. *P* values less than .05 were considered statistically significant. Analyses were performed based on intention-to-treat analysis.

## Results

One hundred twenty-one patients were assessed for eligibility to participate in the study and 100 patients were randomized (Fig. 1). Fifty patients in each group were included in the analysis of the primary outcome. Patients' baseline characteristics and operative times were similar between the 2 groups (Table 1).

The DEX group had approximately a 12-point lower pain score at rest and during motion from postoperative 12 to 21 hours ($P < .05$; Table 2; Figs. 2 and 3). At 21 hours, the mean pain at rest difference (Δ) was −11 points (95% confidence interval [CI], −21 to −2 points; $P = .02$) while the mean pain during motion difference was −15 points (95% CI, −25 to −5 points; $P = .004$). The amount of morphine consumption was similar in both groups overall used and every 12-hour intervals after surgery ($P > .05$), as shown in Table 3.

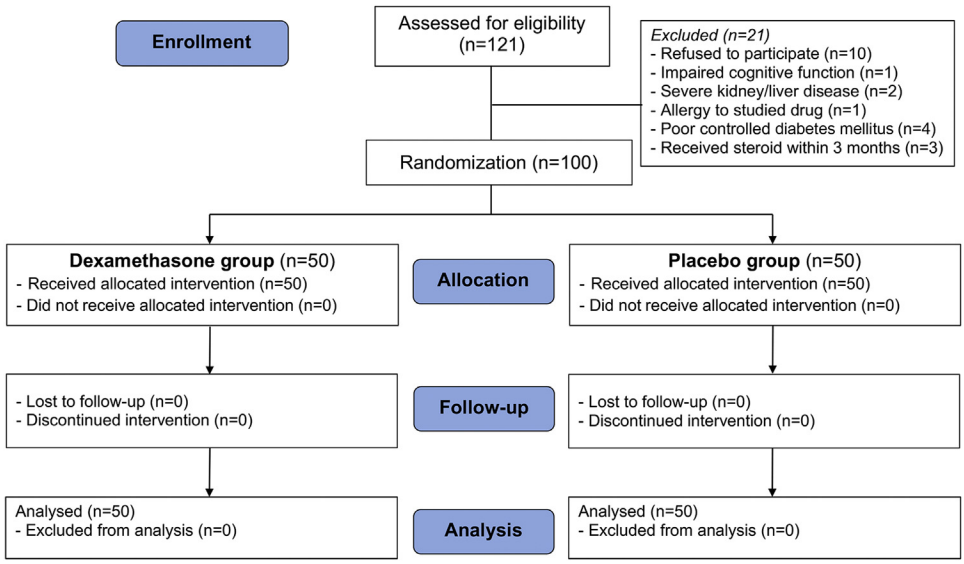


**Fig. 1.** The flowchart shows Consolidated Standards of Reporting Trials (CONSORT) diagram of this study. Data were analyzed on an intention-to-treat basis.

The incidence of PONV was significantly lower in DEX group: 29/50 (58%) vs 42/50 (84%), $P = .008$, as shown in Figure 4. The mean difference in CRP levels at 48 hours postoperation (DEX vs placebo) was −78 mg/L (95% CI, −100 to −58 mg/L, $P < .0001$). Both groups had similar postoperative blood glucose concentrations ($P > .05$) at 24 and 48 hours after surgery (Table 4) as well as similar modified WOMAC scores and ROM of the knee at 6 and 12 weeks postoperation ($P > .05$).

There were no wound infections and the length of hospital stay was similar between both groups: 3.3 ± 0.5 vs 3.4 ± 0.7 days, mean difference, −0.1 (95% CI, −0.4 to 0.2 days; $P = .43$).

## Discussion

Preoperative IV 0.15 mg/kg of DEX significantly reduced pain between 12 and 21 hours after TKA, by a mean of 11 for pain at rest and 15 points during motion when compared with placebo. The effect sizes were approximately 0.5. DEX also reduced the rate of PONV and the blood CRP level.

Corticosteroids reduce pain by inhibiting prostaglandin synthesis, an essential inflammatory mediator, and reduce vascular permeability which results in decreased tissue edema [12]. They also modulate the nociceptive input to the spinal cord, by reducing pain due to postoperative inflammation [2]. Corticosteroids have occasionally been used for reducing postoperative pain in other types of surgery at various doses and different methods of application. Oral surgeons use glucocorticoid to reduce pain and swelling after impacted third molar surgery [13] while general surgeons used methylprednisolone for postoperative pain relief after cholecystectomy [14]. Corticosteroids were introduced several years ago for relieving postoperative pain in total joint arthroplasty but, unfortunately, it is not widely used due to surgeons' concerns and the limited supported evidence. There have been studies reporting the addition of corticosteroids in periarticular anesthetic cocktail injections, which provided better pain relieving after TKA compared to placebo [15,16]. Tammachote el al [17] showed that lumbar epidural triamcinolone injection reduced subacute pain and improved knee function in the first 6 weeks after TKA. Despite these data, there has not been a study that has evaluated the efficacy of IV DEX in controlling pain after TKA using double-blind, randomized trial with postoperative pain as a primary outcome.

In our study, we used 0.15 mg/kg of DEX and the result confirmed its efficacy in controlling pain after TKA. This early postoperative phase is very important because the most severe pain occurs from 6 to 24 hours after TKA [18]. The half-life of DEX is 36-54 hours and its effects were most apparent in the first 24-48 hours [2]. In our study, IV DEX significantly reduced pain between 12 and 21 hours after surgery but the morphine consumption was similar between both groups. Pain scores were similar in both groups in first 12 hours after surgery, which was probably influenced by the analgesic effect of the periarticular multimodal analgesic cocktail, which has been shown to be effective in controlling pain for 12 hours after TKA [19].

A meta-analysis of perioperative DEX found that it was effective as an adjunct in multimodal strategies to reduce postoperative pain and opioid consumption [4]. Unfortunately, this meta-analysis included only 1 orthopedic study investigating pain following total hip arthroplasty patients. Another meta-analysis of various kinds of corticosteroids in TKA included 7 trials but only 1 trial focused on the pain as an outcome. It examined high (>10 mg) and low (<10 mg) dose of DEX equivalence, suggesting a better analgesic effect of the higher dose [20]. Although studies have shown the efficacy of DEX in controlling postoperative pain, the lack of head-to-head comparison with placebo in TKA patients has led surgeons to avoid using corticosteroids to control postoperative pain.

**Table 1**
Demographic Data.

| Variables | Dexamethasone Group (N = 50) | Placebo Group (N = 50) |
|---|---|---|
| Age[a] (y) | 67 ± 8 | 69 ± 9 |
| Sex (male/female)[b] | 8/42 | 6/44 |
| BMI[a] (kg/m$^2$) | 27 ± 4 | 27 ± 4 |
| ASA class[b] I/II/III (n) | 6/40/4 | 4/44/2 |
| Surgical time[a] (min) | 99 ± 17 | 102 ± 14 |
| Preoperative modified WOMAC[a] | 51 ± 13 | 53 ± 10 |
| Preoperative alignment | | |
| Varus/valgus[b] (n) | 41/9 | 46/4 |
| HKA angle in varus knee[a] (°) | 168 ± 5 | 167 ± 6 |
| HKA angle in valgus knee[a] (°) | 186 ± 6 | 186 ± 4 |
| Preoperative knee flexion angle[a] (°) | 126 ± 10 | 123 ± 15 |

BMI, body mass index; ASA, American Society of Anesthesiologists; WOMAC, Western Ontario and McMaster University Osteoarthritis Index; HKA, hip-knee-ankle.
[a] The values are given as the mean and the standard deviation or numbers.
[b] The values are given as the number of patients.

**Table 2**
Mean VAS Score in the First 48 Hours After Operation.

| Parameters | Dexamethasone Group (N = 50)[a] | Placebo Group (N = 50)[a] | Difference[b] | *P* Value |
|---|---|---|---|---|
| VAS at rest (points) | | | | |
| Postop 3 h | 25 ± 31 | 34 ± 31 | −9 (−21 to 3) | .16 |
| Postop 6 h | 30 ± 29 | 30 ± 31 | 0 (−12 to 12) | .98 |
| Postop 9 h | 28 ± 25 | 31 ± 32 | −3 (−14 to 8) | .60 |
| Postop 12 h | 25 ± 24 | 37 ± 33 | −12 (−23 to −0.2) | .046[c] |
| Postop 15 h | 24 ± 22 | 36 ± 31 | −12 (−23 to −1) | .03[c] |
| Postop 18 h | 21 ± 20 | 34 ± 31 | −13 (−24 to −3) | .01[c] |
| Postop 21 h | 20 ± 20 | 31 ± 27 | −11 (−21 to −2) | .02[c] |
| Postop 24 h | 21 ± 21 | 27 ± 26 | −6 (−16 to 3) | .16 |
| Postop 27 h | 22 ± 24 | 26 ± 23 | −4 (−13 to 6) | .46 |
| Postop 30 h | 19 ± 20 | 27 ± 24 | −8 (−17 to 0.8) | .07 |
| Postop 33 h | 19 ± 20 | 25 ± 22 | −6 (−14 to 3) | .19 |
| Postop 36 h | 20 ± 23 | 24 ± 24 | −4 (−13 to 5) | .38 |
| Postop 39 h | 18 ± 22 | 22 ± 22 | −4 (−12 to 5) | .43 |
| Postop 42 h | 18 ± 20 | 19 ± 18 | −1 (−9 to 7) | .76 |
| Postop 45 h | 16 ± 20 | 17 ± 19 | −1 (−8 to 7) | .85 |
| Postop 48 h | 16 ± 20 | 16 ± 19 | 0 (−8 to 8) | .99 |
| VAS during motion (points) | | | | |
| Postop 3 h | 39 ± 32 | 47 ± 35 | −8 (−22 to 5) | .21 |
| Postop 6 h | 43 ± 31 | 47 ± 32 | −4 (−17 to 8) | .47 |
| Postop 9 h | 42 ± 27 | 46 ± 31 | −4 (−16 to 7) | .42 |
| Postop 12 h | 41 ± 23 | 52 ± 32 | −9 (−22 to −0.2) | .047[c] |
| Postop 15 h | 40 ± 23 | 52 ± 32 | −12 (−23 to −1) | .03[c] |
| Postop 18 h | 38 ± 23 | 52 ± 30 | −14 (−24 to −3) | .01[c] |
| Postop 21 h | 36 ± 23 | 51 ± 28 | −15 (−25 to −5) | .004[c] |
| Postop 24 h | 39 ± 23 | 45 ± 28 | −6 (−16 to 4) | .22 |
| Postop 27 h | 40 ± 26 | 48 ± 27 | −8 (−19 to 2) | .13 |
| Postop 30 h | 38 ± 22 | 45 ± 22 | −7 (−16 to 1) | .10 |
| Postop 33 h | 38 ± 24 | 45 ± 24 | −7 (−17 to 3) | .15 |
| Postop 36 h | 36 ± 27 | 42 ± 24 | −6 (−16 to 4) | .23 |
| Postop 39 h | 33 ± 24 | 38 ± 24 | −5 (−15 to 4) | .24 |
| Postop 42 h | 31 ± 23 | 34 ± 23 | −3 (−13 to 6) | .44 |
| Postop 45 h | 29 ± 21 | 34 ± 23 | −5 (−14 to 4) | .25 |
| Postop 48 h | 29 ± 22 | 33 ± 25 | −4 (−13 to 6) | .45 |

VAS, visual analog scale; postop, postoperative.
[a] The values are given as the mean and the standard deviation.
[b] The values are given as the mean, with the 95% confidence interval in parentheses. The differences were calculated using placebo as baseline; a negative value indicates a lower score in the dexamethasone group.
[c] A significant difference between the 2 groups (Student *t*-test).

To our knowledge, no study has thoroughly evaluated the effect of IV DEX in relieving pain whether at rest or during motion after TKA every 3 hours for 48 hours. Most studies have focused on its antiemetic effect and evaluated pain once a day or reported on a mixed patient population undergoing TKA and total hip arthroplasty (Table 5). Lunn et al [7] showed that 125 mg of IV methylprednisolone reduced pain at rest and on motion up to 48 hours after TKA. Their study used an equivalent of 3 times the dose of DEX (≡ 25 mg of

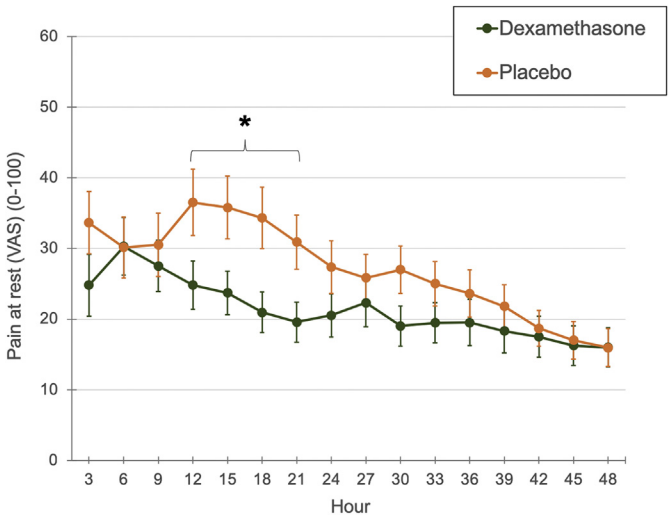


**Fig. 2.** The graph showed mean VAS score for pain at rest in the 2 groups at each time point. The error bars indicated the standard error of the mean. There was a significant difference between the groups from postoperative 12 to 21 hours (*$P < .05$), and also shown in Table 2. VAS, visual analog scale.

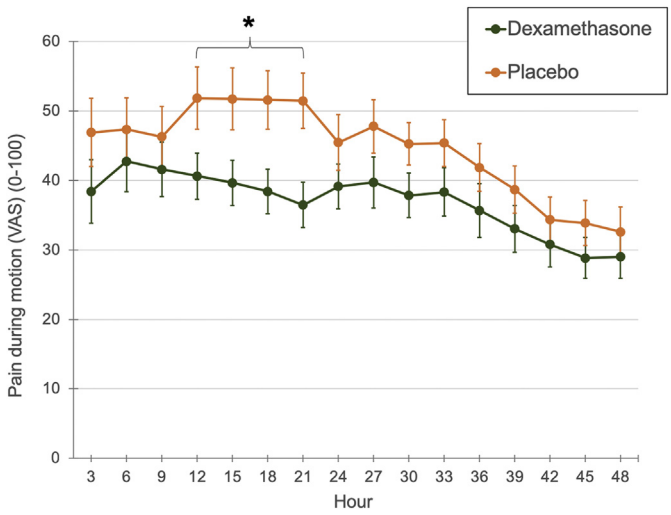


**Fig. 3.** The graph showed mean VAS score for pain during motion in the 2 groups at each time point. The error bars indicated the standard error of the mean. There was a significant difference between the groups from postoperative 12 to 21 hours (*$P < .05$), and also shown in Table 2.

**Table 3**
Morphine Consumption in the First 48 Hours After Operation.

| Parameters | Dexamethasone Group (N = 50) | Placebo Group (N = 50) | Difference[b] | *P* Value |
|---|---|---|---|---|
| Morphine consumption (mg)[a] | | | | |
| Overall (0-48 h) | 7.0 ± 4.7 | 8.1 ± 6.1 | −1.1 (−3.3 to 1.1) | .32 |
| Postop 0-12 h | 2.0 ± 2.5 | 2.2 ± 2.4 | −0.2 (−1.2 to 0.7) | .62 |
| Postop 12-24 h | 1.7 ± 2.2 | 2.2 ± 2.3 | −0.5 (−1.5 to 0.3) | .19 |
| Postop 24-36 h | 1.3 ± 1.8 | 1.6 ± 2.1 | −0.3 (−1.1 to 0.5) | .45 |
| Postop 36-48 h | 1.9 ± 2.1 | 1.9 ± 2.2 | 0 (−0.9 to 0.8) | .96 |

Postop, postoperative.
[a] The values are given as the mean and the standard deviation.
[b] The values are given as the mean, with the 95% confidence interval in parentheses. The differences were calculated using placebo as baseline; a negative value indicates a lower score in the dexamethasone group.

DEX) compared with our study; such a high dose might make the analgesic effect last longer compared to our dose of DEX although the half-life of methylprednisolone is shorter (18-36 hours) [2]. A systematic review of IV corticosteroids in hip or knee arthroplasties reported that they reduced pain during ambulation at 24 hours after surgery [22] and 1 recent study observed that 8 mg of IV DEX after hip and knee arthroplasties resulted in a 20% reduction in pain scores on the first postoperative day [23]. In our study, the reduction in pain level was approximately 30%. Our study confirmed that the analgesic effect of DEX lasted approximately 21 hours; thereafter, the pain between the 2 arms was similar. Another study of multiple doses of DEX injection (at 0, 24, and 48 hours) also reduced postoperative pain in days 1, 2, and 3 [24].

DEX is a well-known effective antiemetic drug in PONV [25] via a direct central activation of the glucocorticoid receptors in the bilateral nuclei tractus solitarii in the medulla [26,27]; meta-analyses confirm reduced PONV rates after TKA [20,28]. We reconfirmed this in our study, with an almost one-third reduction in PONV compared to placebo.

The anti-inflammatory effects of corticosteroids are due to a reduction in systematic inflammatory markers in patients undergoing TKA [8,9,21]; one RCT showed a significant CRP reduction compared to placebo at 24 hours post-TKA [7]. Moreover, 10 mg of IV DEX resulted in an acute (≤48 hours) CRP reduction nearly 50% but this effect was lost by 2 weeks [29] which was consistent with our study. Post-TKA, 48 hours is the time of peak CRP concentration [30].

Many surgeons may be concerned by the adverse effects of corticosteroids on many organ systems, especially hyperglycemia, suppression of the immune system, and inhibition of the hypothalamic-pituitary-adrenal (HPA) axis. Several meta-analyses

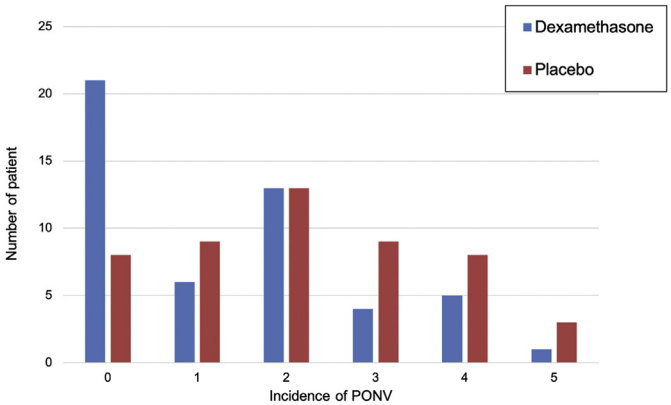


**Fig. 4.** The histogram showed the incidence of postoperative nausea and vomiting (PONV).

**Table 4**
Postoperative Outcomes.

| Parameters | Dexamethasone Group (N = 50)[a] | Placebo Group (N = 50)[a] | Difference[b] | *P* Value |
|---|---|---|---|---|
| CRP level (mg/L) | | | | |
| Preop | 3 ± 3 | 3 ± 4 | 0 (−1.5 to 1.4) | .95 |
| Postop 48 h | 89 ± 51 | 167 ± 53 | −78 (−100 to −58) | <.0001[c] |
| Modified WOMAC (points) | | | | |
| Preop | 51 ± 13 | 53 ± 10 | −2 (−6 to 3) | .55 |
| Postop wk 6 | 26 ± 7 | 26 ± 6 | 0 (−3 to 2) | .73 |
| Postop wk 12 | 15 ± 7 | 15 ± 6 | 0 (−2 to 3) | .55 |
| Knee flexion (°) | | | | |
| Preop | 126 ± 10 | 123 ± 15 | 3 (−1 to 9) | .14 |
| Postop wk 6 | 130 ± 7 | 127 ± 7 | 3 (−1 to 5) | .06 |
| Postop wk 12 | 135 ± 5 | 134 ± 5 | 1 (−1 to 3) | .21 |
| Knee extension (°) | | | | |
| Preop | 0.1 ± 4 | 0.3 ± 4 | −0.2 (−1.8 to 1.4) | .80 |
| Postop wk 6 | 0.2 ± 0.9 | 0.5 ± 1.4 | −0.3 (−0.7 to 0.2) | .32 |
| Postop wk 12 | 0.2 ± 0.8 | 0.2 ± 0.9 | 0 (−0.4 to 0.3) | .73 |
| Blood sugar (mg/dL) | | | | |
| Preop (FBS) | 102 ± 16 | 105 ± 22 | −3 (−11 to 4) | .40 |
| Postop 24 h (RBS) | 133 ± 29 | 125 ± 27 | 8 (−3 to 20) | .13 |
| Postop 48 h (RBS) | 118 ± 25 | 121 ± 25 | −3 (−13 to 6) | .49 |

CRP, C-reactive protein; WOMAC, Western Ontario and McMaster University Osteoarthritis Index; preop, preoperative; postop, postoperative.
[a] The values are given as the mean and the standard deviation.
[b] The values are given as the mean, with the 95% confidence interval in parentheses. The differences were calculated using placebo as baseline; a negative value indicates a lower score in the dexamethasone group.
[c] A significant difference between the 2 groups (Student *t*-test). The blood sugar level at preoperation was fasting blood sugar (FBS) but postoperative blood sugar level was random blood sugar (RBS).

indicate that IV DEX is associated with hyperglycemia on the first postoperative day in a dose-dependent manner [20,31]. Corticosteroids provide a substrate for oxidative stress metabolism increasing hepatic glucose production, lipolysis, and proteolysis [32], and higher DEX doses resulted in greater hyperglycemia [33]. One study compared type 2 diabetics to nondiabetic patients and showed similar postoperative hyperglycemia after administration of 8 mg of IV DEX [34]. Our study, which excluded patients with poorly controlled diabetes mellitus, found similar random glucose concentrations at 24 hours after injection in both groups. However, corticosteroids should be used cautiously in patients with diabetes mellitus who need glucose monitoring.

Theoretically, corticosteroids could inhibit the inflammatory phase of wound healing; this phase is characterized by cellular migration and increased vascular permeability and also reduced concentrations of insulin-like growth factor-1 and growth factor-β, both of which are important cellular signals for re-epithelialization of wounds, collagen deposition, angiogenesis, and fibrogenesis [35]. This coupled with steroid-induced immunosuppression may increase the risk of wound infection. However, meta-analyses and reviews found that single-dose intraoperative DEX did not increase the risk of surgical site infections [4,20,28,31,36]. Vuorinen et al [37] analyzed 19,000 hip and knee arthroplasties, including the revisions, and reported that the use of 5-10 mg of DEX did not increase the rate of postoperative periprosthetic joint infection.

Our study had some limitations. First, the sample size was small; with 50 patients per arm, our statistical power to detect rare events such as periprosthetic infection was limited. Second, we prescribed multimodal pain control, which included an anesthetic cocktail injection and IV ketorolac to protect patients from severe pain and this may have resulted in reduced morphine use by both arms but we were able to detect a difference in pain score. The average pain at rest was approximately 30-40 points. The patients might feel more pain but insufficient to request the extra analgesic drug. Aubrun et al observed that the relationship of VAS and morphine

**Table 5**
The Previous Randomized Controlled Trials of Intravenous Corticosteroid Injection in Unilateral TKA.

| Study | Number | Study Intervention | Primary Outcome | Pain Reduction | Opioid Consumption | PONV | CRP Level |
|---|---|---|---|---|---|---|---|
| Lunn et al [7] | 48 | Methylprednisolone 125 mg vs placebo before spinal anesthesia | Pain during walking 24 h (VAS at 2, 4, 6, 24, 28, 32, and 48 h) | Lower overall VAS at 2-48 h and VAS during walking at 2-32 h | Less oxycodone consumption in 24 h | Lower number of patients vomiting and requiring Ond at PO 0-24 h | Lower CRP level at 24 h |
| Koh et al [5] | 269 | DEX 10 mg + Ram vs Ram only at 1 h before surgery | Incidence of PONV | Lower VAS at PO 6-24 h | Less fentanyl consumption in 72 h | Lower incidence of PONV during 72 h<br>Lower use of antiemetic drug | NA |
| Backes et al [6] | 120 (47 THA, 73 TKA) | (1) 2 Doses of DEX 10 mg (prior induction and PO 24 h) + Ond vs (2) DEX 10 mg + Ond vs (3) Ond | Length of hospital stay | 1, 2 vs 3—lower VAS in 48 h<br>1 vs 2—no difference in VAS | 1,2 vs 3—less hydrocodone used in 48 h<br>1vs 2—less hydrocodone used in the second day | Lower antiemetic drug at PO days 0, 1, 2<br>Lower antiemetic drug when second dose of DEX was added at PO day 2 | NA |
| Xu et al [21] | 108 | 2 Doses of DEX 10 mg (after GA and at inpatient unit) vs placebo | Inflammation markers (CRP and IL-6) | Lower VAS at 24 h | Less oxycodone and parecoxib used in 72 h | Lower incidence of PONV (17% vs 44%) | Lower CRP and IL-6 at 24, 48, and 72 h |
| Present study | 100 | DEX 0.15 mg/kg vs placebo before surgery | Pain level (VAS every 3 h until 48 h) | Lower VAS at rest and on motion 12-21 h | Similar morphine consumption in 48 h | Lower incidence of PONV (58% vs 84%) | Lower CRP level at 48 h |

TKA, total knee arthroplasty; THA, total hip arthroplasty; DEX, dexamethasone; Ram, ramosetron; Ond, ondansetron; PO, postoperative; PONV, postoperative nausea and vomiting; GA, general anesthesia; VAS, visual analog scale; CRP, C-reactive protein; IL-6, interleukin-6.

dose was like a sigmoid curve. The morphine consumption was not correlated well to the pain severity when the patients had mild pain or extremely severe pain [38]. Third, we investigated hyperglycemia with only 2 random glucose samples at 24 and 48 hours post-TKA; thus, our sensitivity for detecting hyperglycemia was quite low. Finally, patients received different doses of ketorolac due to drug recommendation. We did subgroup analysis and observed 41 patients received full dose (30 mg) of ketorolac while 59 patients received half dose (15 mg) of ketorolac. The difference between mean of VAS in between DEX group and placebo group was higher in the patients who received half dose of ketorolac. The analgesic effect of full dose of ketorolac might obscure the effect of DEX, and this finding emphasized the benefit of DEX to reduce pain in patients who could not get full regimen of multimodal analgesia.

In conclusion, combined with multimodal pain regimens in TKA, a single preoperative IV DEX reduced pain whether at rest and during motion during a tight window between 12 and 21 hours post-TKA and reduced the rate of nausea/vomiting and inflammatory response in postoperative acute period. Thus, single-dose IV DEX represents a promising approach in postoperative pain management and may be suitable for patients with contraindication to multimodal pain regimens. More research is needed to define the optimal doses of IV DEX and its duration of administration.

## Acknowledgments

We thank Bob Taylor, PhD, for reviewing the article and language help. We also thank all participants for providing the data used in this study. Our institution (Thammasat University) provided the funding for this study.

## References

[1] Bourne RB, Chesworth BM, Davis AM, Mahomed NN, Charron KD. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? Clin Orthop Relat Res 2010;468:57–63.
[2] Salerno A, Hermann R. Efficacy and safety of steroid use for postoperative pain relief. Update and review of the medical literature. J Bone Joint Surg Am 2006;88:1361–72.
[3] Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, et al. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2014;118:85–113.
[4] De Oliveira Jr GS, Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology 2011;115:575–88.
[5] Koh IJ, Chang CB, Lee JH, Jeon YT, Kim TK. Preemptive low-dose dexamethasone reduces postoperative emesis and pain after TKA: a randomized controlled study. Clin Orthop Relat Res 2013;471:3010–20.
[6] Backes JR, Bentley JC, Politi JR, Chambers BT. Dexamethasone reduces length of hospitalization and improves postoperative pain and nausea after total joint arthroplasty: a prospective, randomized controlled trial. J Arthroplasty 2013;28(8 Suppl):11–7.
[7] Lunn TH, Kristensen BB, Andersen LO, Husted H, Otte KS, Gaarn-Larsen L, et al. Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: a randomized, placebo-controlled trial. Br J Anaesth 2011;106:230–8.
[8] Jules-Elysee KM, Lipnitsky JY, Patel N, Anastasian G, Wilfred SE, Urban MK, et al. Use of low-dose steroids in decreasing cytokine release during bilateral total knee replacement. Reg Anesth Pain Med 2011;36:36–40.
[9] Jules- Elysee KM, Wilfred SE, Memtsoudis SG, Kim DH, YaDeau JT, Urban MK, et al. Steroid modulation of cytokine release and desmosine levels in bilateral total knee replacement: a prospective, double-blind, randomized controlled trial. J Bone Joint Surg Am 2012;94:2120–7.
[10] Crandell JT. Perineal pruritus after the administration of iv dexamethasone. Can J Anaesth 2004;51:398.
[11] Kuptniratsaikul V, Rattanachaiyanont M. Validation of a modified Thai version of the Western Ontario and McMaster (WOMAC) osteoarthritis index for knee osteoarthritis. Clin Rheumatol 2007;26:1641–5.
[12] Vyvey M. Steroids as pain relief adjuvants. Can Fam Physician 2010;56:1295–7.
[13] Skjelbred P, Lokken P. Reduction of pain and swelling by a corticosteroid injected 3 hours after surgery. Eur J Clin Pharmacol 1982;23:141–6.
[14] Schulze S, Moller IW, Bang U, Rye B, Kehlet H. Effect of combined prednisolone, epidural analgesia and indomethacin on pain, systemic response

and convalescence after cholecystectomy. Acta Chir Scand 1990;156:203–9.
[15] Tsukada S, Wakui M, Hoshino A. The impact of including corticosteroid in a periarticular injection for pain control after total knee arthroplasty: a double-blind randomised controlled trial. Bone Joint J 2016;98-b:194–200.
[16] Kwon SK, Yang IH, Bai SJ, Han CD. Periarticular injection with corticosteroid has an additional pain management effect in total knee arthroplasty. Yonsei Med J 2014;55:493–8.
[17] Tammachote N, Seangleulur A, Kanitnate S. Lumbar epidural corticosteroid injection reduces subacute pain and improves knee function in the first six weeks after total knee arthroplasty: a double-blinded randomized trial. J Bone Joint Surg Am 2018;100:950–7.
[18] Valeberg BT, Hovik LH, Gjeilo KH. Relationship between self-reported pain sensitivity and pain after total knee arthroplasty: a prospective study of 71 patients 8 weeks after a standardized fast-track program. J Pain Res 2016;9:625–9.
[19] Tammachote N, Kanitnate S, Manuwong S, Yakumpor T, Panichkul P. Is pain after TKA better with periarticular injection or intrathecal morphine? Clin Orthop Relat Res 2013;471:1992–9.
[20] Xing LZ, Li L, Zhang LJ. Can intravenous steroid administration reduce postoperative pain scores following total knee arthroplasty?: a meta-analysis. Medicine (Baltimore) 2017;96:e7134.
[21] Xu B, Ma J, Huang Q, Huang ZY, Zhang SY, Pei FX. Two doses of low-dose perioperative dexamethasone improve the clinical outcome after total knee arthroplasty: a randomized controlled study. Knee Surg Sports Traumatol Arthrosc 2018;26:1549–56.
[22] Hartman J, Khanna V, Habib A, Farrokhyar F, Memon M, Adili A. Perioperative systemic glucocorticoids in total hip and knee arthroplasty: a systematic review of outcomes. J Orthop 2017;14:294–301.
[23] Dissanayake R, Du HN, Robertson IK, Ogden K, Wiltshire K, Mulford JS. Does dexamethasone reduce hospital readiness for discharge, pain, nausea, and early patient satisfaction in hip and knee arthroplasty? A randomized, controlled trial. J Arthroplasty 2018;33:3429–36.
[24] Xu H, Zhang S, Xie J, Lei Y, Cao G, Pei F. Multiple doses of perioperative dexamethasone further improve clinical outcomes after total knee arthroplasty: a prospective, randomized, controlled study. J Arthroplasty 2018;33:3448–54.
[25] Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. Anesth Analg 2000;90:186–94.
[26] Chu CC, Hsing CH, Shieh JP, Chien CC, Ho CM, Wang JJ. The cellular mechanisms of the antiemetic action of dexamethasone and related glucocorticoids against vomiting. Eur J Pharmacol 2014;722:48–54.
[27] Ho CM, Ho ST, Wang JJ, Tsai SK, Chai CY. Dexamethasone has a central antiemetic mechanism in decerebrated cats. Anesth Analg 2004;99:734–9.
[28] Chen P, Li X, Sang L, Huang J. Perioperative intravenous glucocorticoids can decrease postoperative nausea and vomiting and pain in total joint arthroplasty: a meta-analysis and trial sequence analysis. Medicine (Baltimore) 2017;96:e6382.
[29] Brekke AC, Amaro EJ, Posey SL, Engstrom SM, Polkowski GG, Schoenecker JG. Do corticosteroids attenuate the peri-operative acute phase response after total knee arthroplasty? J Arthroplasty 2019;34:27–35.
[30] Thienpont E, Grosu I, Jonckheere S, Yombi JC. C-reactive protein (CRP) in different types of minimally invasive knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2013;21:2603–10.
[31] Yue C, Wei R, Liu Y. Perioperative systemic steroid for rapid recovery in total knee and hip arthroplasty: a systematic review and meta-analysis of randomized trials. J Orthop Surg Res 2017;12:100.
[32] van Raalte DH, Ouwens DM, Diamant M. Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? Eur J Clin Invest 2009;39:81–93.
[33] Low Y, White WD, Habib AS. Postoperative hyperglycemia after 4- vs 8-10-mg dexamethasone for postoperative nausea and vomiting prophylaxis in patients with type II diabetes mellitus: a retrospective database analysis. J Clin Anesth 2015;27:589–94.
[34] Nazar CE, Echevarria GC, Lacassie HJ, Flores RA, Munoz HR. [Effects on blood glucose of prophylactic dexamethasone for postoperative nausea and vomiting in diabetics and non-diabetics]. Rev Med Chil 2011;139:755–61.
[35] Bolac CS, Wallace AH, Broadwater G, Havrilesky LJ, Habib AS. The impact of postoperative nausea and vomiting prophylaxis with dexamethasone on postoperative wound complications in patients undergoing laparotomy for endometrial cancer. Anesth Analg 2013;116:1041–7.
[36] Assante J, Collins S, Hewer I. Infection associated with single-dose dexamethasone for prevention of postoperative nausea and vomiting: a literature review. AANA J 2015;83:281–8.
[37] Vuorinen MA, Palanne RA, Makinen TJ, Leskinen JT, Huhtala H, Huotari KA. Infection safety of dexamethasone in total hip and total knee arthroplasty: a study of eighteen thousand, eight hundred and seventy two operations. Int Orthop 2019;43:1787–92.
[38] Aubrun F, Langeron O, Quesnel C, Coriat P, Riou B. Relationships between measurement of pain using visual analog score and morphine requirements during postoperative intravenous morphine titration. Anesthesiology 2003;98:1415–21.