CLINICAL ARTICLE

Combined Application of Dexamethasone and Tranexamic Acid to Reduce the Postoperative Inflammatory Response and Improve Functional Outcomes in Total Hip Arthroplasty

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Objective: To evaluate the efficacy and safety of combined use of tranexamic acid (TXA) and dexamethasone (DEX) for anti-inflammatory and clinical outcomes after total hip arthroplasty (THA).

Methods: A total of 100 patients were included in this randomized, controlled study. Patients in the TXA + DEX group were administered TXA at a dose of 15 mg/kg, which was repeated 3 h after THA, and received 20 mg DEX. In contrast, patients in the TXA group were administered TXA at a dose of 15 mg/kg, which was repeated at 3 h postoperatively. C-reactive protein (CRP), interleukin-6 (IL-6) and pain levels, incidence of postoperative nausea and vomiting (PONV), total blood loss and transfusion rates, postoperative fatigue, range of motion (ROM), length of hospital stay (LOS), analgesic rescue and antiemetic rescue consumption, and complications were compared in both groups.

Results: The CRP and IL-6 levels were lower in the TXA + DEX group than in the TXA group (all $P < 0.001$) at 24 h, 48 h, and 72 h postoperatively. Patients in the TXA + DEX group had lower pain scores at rest and walking at 24 h postoperatively (all $P < 0.001$). In the TXA + DEX group, the incidence of PONV was lower ($P = 0.005$), postoperative fatigue ($P < 0.001$) was reduced, and analgesia and antiemetic rescue consumption were also reduced. The total blood loss, transfusion rate, LOS and hip ROM were similar in the two groups. There was no thrombosis, infection, or gastrointestinal bleeding in either group.

Conclusion: Compared to TXA alone, the combination of TXA + DEX can reduce postoperative inflammatory response, relieve pain, and reduce PONV and fatigue, without increasing the risk of complications. Therefore, the present study suggested that the combination of TXA + DEX is an effective and safe accelerated rehabilitation strategy for patients receiving primary unilateral THA.

Key words: Clinical outcomes; Dexamethasone; Total hip arthroplasty; Tranexamic acid

Background

Total hip arthroplasty (THA) is one of the most effective orthopaedic surgeries, which reconstructs the lower limb line, relieves pain, and improves joint function, but it also causes postoperative acute anemia and blood transfusion-related complications[1–3]. At the same time, surgical trauma in THA can cause severe postoperative inflammation reactions[4–6], and is often associated with severe postoperative pain and fatigue[7,8], increased incidence of postoperative nausea and vomiting (PONV)[9,10], limited range of motion (ROM)[11], and prolonged hospital stay[12]. In addition, inadequate perioperative management is directly related to poor

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patient satisfaction and may hinder recovery after surgery for THA[13,14]. Therefore, it is important to control the postoperative blood loss and inflammatory response of THA.

In recent 10 years, surgical techniques and perioperative management guidelines have made gratifying progress in THA, promoting the rapid recovery of patients. Tranexamic acid (TXA), a synthetic analog of lysine, inhibits fibrinolysis by competitively blocking the lysine binding site of plasminogen, often used for joint replacement to reduce perioperative blood loss[15–17], and it has anti-inflammatory effects[6,18]. Dexamethasone (DEX), with a strong anti-inflammatory agent, has been widely used to reduce inflammatory markers[19–21], prevent PONV[22,23], and relieve postoperative pain and fatigue in various perioperative periods[24–26]. Many previous randomized controlled trials (RCT) and meta-analyses have demonstrated the effectiveness of DEX in preventing inflammatory stress, without the disadvantages of the wound and gastrointestinal bleeding complications in THA[20,27]. The combined application of DEX and TXA has been reported in a few studies; however, the additional effects of the combined administration are not completely clear.

The purpose of this randomized controlled trial was to assess the combined application DEX and TXA in primary THA in terms of: (i) the level of postoperative blood loss and inflammatory markers (C-reactive protein [CRP] and interleukin-6 [IL-6]); (ii) whether the combined application of DEX and TXA reduces PONV and provides additional analgesic effect; (iii) whether the combined application of DEX and TXA reduces postoperative fatigue; (iv) whether the combined application of DEX and TXA reduces the length of stay (LOS) and improves ROM; and (v) whether the combined application of DEX and TXA increases the risk of adverse effects.

Materials and Methods

Patients and Design

This work was reported in line with the Consolidated Standards of Reporting Trials (CONSORT) Guidelines. All patients who received primary unilateral THA were enrolled in the study. Exclusion criteria were as follows: rheumatoid arthritis, patients with infection, allergy to DEX and TXA, body mass index (BMI) > 30 kg/m^2, preoperative anemia (hemoglobin [Hb] level < 12 g/dL for women and < 13 g/dL for men), age ≤18 years or ≥ 80 years, alcohol or drug abuse, any glucocorticoid given within 3 months prior to surgery, and severe heart, liver and kidney dysfunction. Patients were randomly assigned to the TXA and DEX + TXA groups and randomization was blinded and performed using a sealed envelope at a 1:1 ratio to open before surgery. A computer-generated random number table was used to generate a stratified randomization plan.

After institutional ethics committee approval and written informed consent was obtained from each patient.

Intervention

Patients in the TXA group (n = 50) were administered TXA at a dose of 15 mg/kg intravenously (TXA, Chongqing Lummy Pharmaceutical China) at 10 min before skin incision and again 3 h after the THA. In addition, to support this double-blind study, patients in the TXA group were given 4 mL of normal saline solution before anesthesia induction. Patients in the TXA + DEX group (n = 50) were administered TXA at a dose of 15 mg/kg at 10 min before skin incision and again at 3 h postoperatively after THA, and received one intravenous injection of 20 mg dexamethasone (4 mL, Tianjin Kingyork group, China) before anesthesia induction. Anesthesiologists and nurses were not involved in the study, and the patients, surgeons, data controllers, and statisticians were blinded to the treatment.

Surgical Technique

All surgeries were performed by a senior surgeon in the same laminar airflow operating room. All procedures were conducted under general anesthesia using a posterolateral surgical approach. All total hip prostheses were uncemented prostheses, and a drainage catheter was not used. A periarticular injection of 0.2% ropivacaine (100 mL) was given before the incision was closed.

Postoperative Care

After surgery, the patients were transferred to the post-anesthesia care unit. After patients returned to the inpatient ward, a cold pack was used at the surgical site. Intermittent pneumatic compression devices were typically applied to patients' lower leg until they started walking. All patients performed daily functional training and walking training with the supervision and assistance of a physiotherapist.

Management strategies for pain and PONV were as follows. Before surgery, 200 mg q 12 h celecoxib was administered orally for preemptive analgesia. After surgery, patients' pain was assessed using a 0–10 visual analog scale (VAS). When VAS was greater than four, oral oxycodone (10 mg q 8 h) was added. If the patient reported severe pain (score greater than 6), then the muscle pethidine hydrochloride (100 mg) was administered. When the patient had two or more PONV or severe nausea (VAS > 4), intramuscular injection of metoclopramide (10 mg) was used as a first-line treatment.

All patients were injected subcutaneously with low molecular weight heparin (0.2 mL, 2000 IU; Clexane, Sanofi-Aventis, France) 6 h after surgery, with full doses repeated at 24 h intervals (0.4 mL, 4000 IU). After discharge, rivaroxaban (10 mg QD; Xarelto, Bayer, Germany) was administered orally for 10 days to prevent thrombosis. Doppler ultrasonography is often used to detect deep vein thrombosis (DVT) at discharge as well as at 3 months, or any time a patient is clinically suspected of having DVT. Pulmonary embolism (PE) was diagnosed by chest CT scan.

Outcome Measurements

The primary outcome included inflammatory marker levels (CRP and IL-6) at 24 h, 48 h, and 72 h postoperatively. The amount of pain and analgesics (oxycodone and meperidine hydrochloride) were recorded to evaluate the analgesic effect. Pain levels were assessed using the VAS (0 for no pain and 10 for the most severe pain) at 24 h, 48 h and 72 h postoperatively at rest and during walking training. The incidence of PONV and the consumption of antiemetics (metoclopramide) were recorded postoperatively. The secondary outcomes included total blood loss and transfusion requirements. Fatigue and ROM were assessed individually using the identity results fatigue scale (ICFS) and a goniometer at the time of discharge surgery. The LOS and complications in both groups were also carefully recorded. The total blood loss was assessed using the Gross formula. The need for blood transfusion was based on Chinese Ministry of Health guidelines, at Hb level <70 g/L or 70–100 g/L with symptoms of anemia (i.e. altered mental state, dizziness, and palpitations).

Statistical Analysis

The sample was analyzed using PASS 2011 software (NCSS, LLC, Kaysville, UT, USA), with a one-way analysis of variance design. As previously described by Koh *et al.*[24], the mean VAS scores were 2.4 when using dexamethasone. To detect an average decrease in the VAS score of 1.0, with a power of 0.90 and a significance level of 0.05, 42 patients in each group were required. At the same time, the study assumes that there is a 10% exclusion rate; thus, the minimum sample size for each group is 47. Therefore, we decided to include 50 patients in each group.

Statistical analyses were assessed using SPSS version 20.0 software (SPSS, Chicago, IL, USA). Continuous variables were given in 95% confidence intervals with mean ± standard deviation. The Wilcoxon Mann–Whitney *U*-test was used if the numerical variables were not normally distributed or anisotropic. The Pearson χ^2-test or the Fisher exact test was used to compare the categorical variables. A *P*-value of < 0.05 was considered statistically significant.

Results

Patient Demographics

109 consecutive patients were eligible for screening. The follow-up period was 3 months. Based on the exclusion criteria, 6 patients were excluded, and 3 patients refused to participate. Therefore, 100 patients were included in the current study, 50 were randomized into the TXA group, and 50 were randomized to the TXA + DEX group (Fig. 1). All patients completed the entire follow-up of primary and secondary outcomes. Baseline characteristics between the two groups are presented in Table 1, without statistical differences.

Inflammation Markers

The levels of CRP and IL-6 in the two groups were higher than those before surgery. The mean CRP levels peaked at 48 h after surgery in the two groups, but the CRP levels in the TXA + DEX group were lower than those in the TXA group 24 h ($P < 0.001$), 48 h ($P < 0.001$), and 72 h ($P < 0.001$) after surgery. The mean level of IL-6 in the TXA group peaked at 24 h after surgery and peaked at 48 h after surgery in the TXA + DEX group. The levels of IL-6 in the TXA + DEX group were lower than those in the TXA group 24 h ($P < 0.001$), 48 h ($P < 0.001$), and 72 h ($P < 0.001$) after surgery (Figs 2 and 3).

Pain and Analgesic Rescue

The VAS pain scores in both groups were lower than before surgery. However, patients in group TXA + DEX had less pain than the TXA group at 24 h after surgery, both at rest ($P < 0.001$) and during walking ($P < 0.001$). However, the VAS pain scores of the two groups during rest and walking were similar 48 h and 72 h after surgery (Figs 4 and 5).

The number of patients requiring oxycodone in the TXA + DEX group was lower ($P = 0.013$) and the overall oxycodone consumption was lower ($P < 0.001$) compared with the TXA group. Similarly, the number of patients requiring meperidine hydrochloride was lower in the TXA + DEX group ($P = 0.016$), and the total meperidine hydrochloride consumption was lower in the TXA + DEX group ($P < 0.001$) (Table 2).

Postoperative Nausea and Vomiting and Antiemetic Rescue

The incidence of PONV was lower in the TXA + DEX group ($P = 0.005$) compared with the TXA group (Table 3). The number of patients requiring metoclopramide was lower in the TXA + DEX group ($P = 0.015$) and the total consumption of metoclopramide was less compared with the TXA group ($P < 0.001$) (Table 2).

Total Blood Loss and Transfusion Requirements

There was no significant difference in total blood loss ($P = 0.628$), maximum Hb drop ($P = 0.321$), maximum hematocrit drop ($P = 0.588$), and transfusion rates ($P = 1.00$) (Table 3).

Fatigue, Hip Range of Motion, Length of Hospital Stay, and Complications

The ICFS score was lower in the TXA + DEX group than in the TXA group, and the difference was statistically significant ($P < 0.001$). However, the hip ROM at the time of discharge ($P < 0.001$), LOS ($P = 0.591$), and operation time ($P = 0.459$) were similar between the two groups (Table 3). There were also no side effects of wound infection and gastrointestinal bleeding in the TXA + DEX and the TXA group. (Table 4).

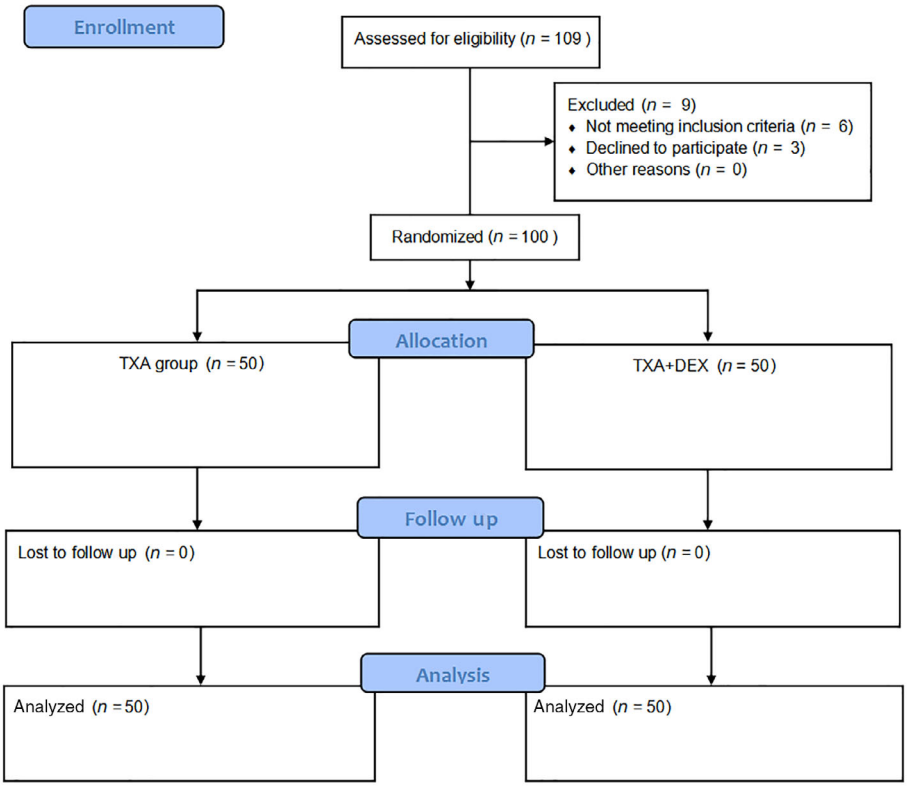

Fig. 1 CONSORT flow diagram. TXA, tranexamic acid; DEX, dexamethasone.

TABLE 1 Baseline data

Parameter	TXA group	TXA + DEX group	*P*
Age (y)	67.36 ± 3.49	67.50 ± 4.40	0.860
Female/Male (*n*)	27/23	25/25	0.689
Height (cm)	161.00 ± 7.15	160.22 ± 7.56	0.597
Weight (kg)	65.76 ± 4.86	64.98 ± 4.98	0.429
BMI (kg/m^2)	25.46 ± 2.34	25.44 ± 2.77	0.983
Diagnosis			0.539
OA (*n*)	32	29	
ONFH (*n*)	18	21	
ASA scores	2.02 ± 0.22	2.04 ± 0.67	0.877
Pre-Hb level (g/L)	13.52 ± 0.51	13.65 ± 0.45	0.160
Pre- Hct level (L/L)	40.09 ± 1.52	40.32 ± 1.80	0.499
Pre-ROM (°)	94.32 ± 4.13	93.96 ± 3.83	0.652
Pre-ICFS scores	64.94 ± 5.47	63.24 ± 5.36	0.120
Pre-CRP (mg/L)	3.22 ± 0.78	3.46 ± 0.83	0.135
Pre-IL-6 (pg/L)	4.47 ± 0.91	4.30 ± 0.78	0.139
Pre-VAS scores at rest	3.48 ± 1.16	3.56 ± 1.20	0.736
Pre-VAS scores at walking	5.16 ± 0.79	5.28 ± 0.86	0.469

ASA, America anesthesia association; BMI, body mass index; CRP, C-reactiveprotein; DEX, dexamethasone; Hb, hemoglobin; Hct, hematocrit; ICFS, Identity Consequence Fatigue Scale; IL-6, interleukin 6; *n*, number; OA, osteoarthritis; ONFH, osteonecrosis of the femoral head; ROM, range of motion; TXA, tranexamic acid; VAS, visual analog scale; y, years. *P*-value was analyzed by Student *t*-test and Pearson χ^2-test.

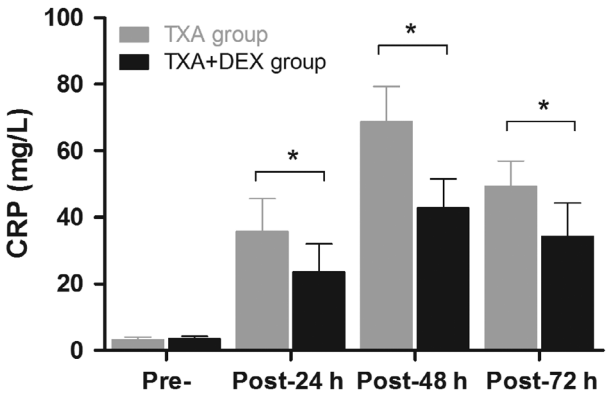

Fig. 2 The level of CRP in the two groups. Pre-, preoperative, post, postoperative. *$P < 0.001$. TXA, tranexamic acid; DEX, dexamethasone.

Discussion

In the current study, we investigated whether the combined use of TXA + DEX could have the additional effect of reducing the postoperative inflammatory response and improving functional outcomes. To the best of our knowledge, there are few similar studies evaluating the effectiveness and safety of combined applications of TXA and DEX in patients undergoing THA. The most important finding of the present study was that the combination of TXA + DEX

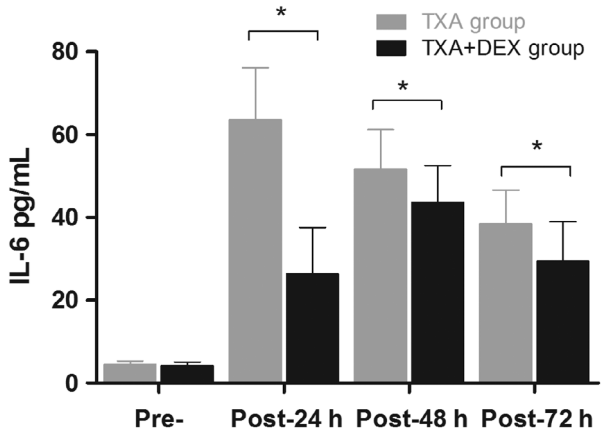

Fig. 3 The level of IL-6 in the two groups. Pre-, preoperative, post, postoperative. *$P < 0.001$. TXA, tranexamic acid; DEX, dexamethasone.

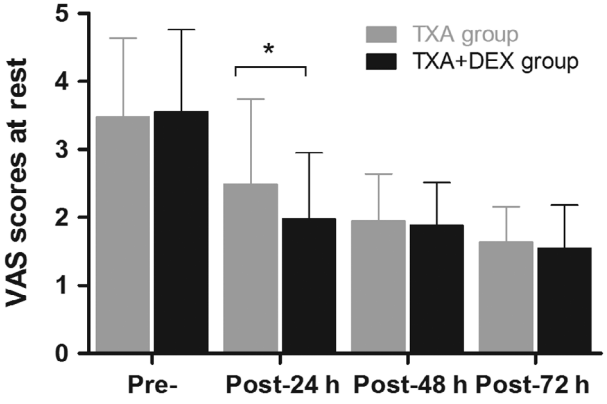

Fig. 4 The level of VAS scores at rest in the two groups. Pre-, preoperative; post, postoperative. *$P < 0.001$. TXA, tranexamic acid; DEX, dexamethasone.

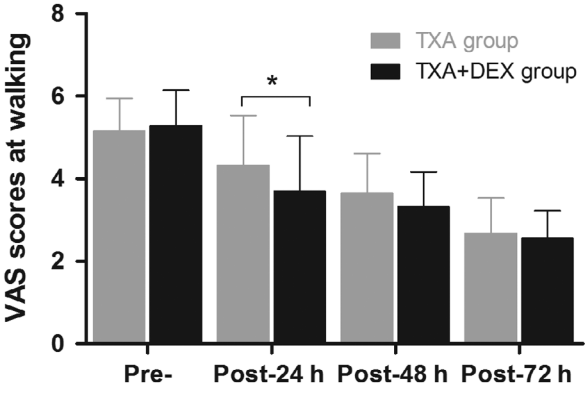

Fig. 5 The level of VAS scores at walking in the two groups. Pre-, preoperative; post, postoperative.*$P < 0.001$. TXA, tranexamic acid; DEX, dexamethasone.

TABLE 2 Analgesic rescue and antiemetic rescue

Parameter	TXA group	TXA + DEX group	*P*
Oxycodone			
Number of patients requiring (*n*)	19	8	0.013
Total dose (mg)	440 (0–30)	120 (0–20)	<0.001
Average dose (mg)	8.80 ± 1.36	2.40 ± 1.67	<0.001
Meperidine hydrochloride			
Number of patients requiring (*n*)	8	2	0.016
Total dose (mg)	800 (0–100)	200 (0–100)	<0.001
Average dose (mg)	16.00 ± 5.23	4.00 ± 2.80	0.046
Metoclopramide			
Number of patients requiring (*n*)	16	6	0.015
Total dose (mg)	190 (0–20)	60 (0–10)	<0.001
Average dose (mg)	3.80 ± 0.85	1.20 ± 0.46	0.009

DEX, dexamethasone; *n*, number; TXA, tranexamic acid. *P*-value was analyzed by Student *t*-test and Pearson χ^2-test or Fisher's exact test.

TABLE 3 Clinical outcomes

Parameter	TXA group	TXA + DEX group	*P*
Total blood loss (mL)	959.28 ± 59.00	948.04 ± 86.99	0.628
Maximum Hb drop (g/L)	3.20 ± 0.59	3.08 ± 0.61	0.321
Maximum Hct drop (L/L)	8.02 ± 1.95	7.80 ± 2.20	0.588
Transfusion rates (*n*)	1	0	1.00
PONV (*n*)	18	6	0.005
ROM (°)	104.90 ± 5.03	106.56 ± 5.16	0.106
ICFS scores	71.04 ± 5.07	79.84 ± 6.44	< 0.001
LOS (day)	5.02 ± 0.62	4.94 ± 0.84	0.591
Operation time (min)	67.96 ± 2.98	67.82 ± 2.93	0.459

DEX, dexamethasone; Hb, hemoglobin; Hct, hematocrit; ICFS, identity-consequence-fatigue-scale; LOS, length of hospital stay; PONV, postoperative nausea and vomiting; ROM, range of motion; TXA, tranexamic acid. *P* value was analyzed by Student-*t*-test and Pearson chi-square test or Fisher's exact test.

reduced postoperative CRP and IL-6 levels, provided additional analgesic effects, and reduced the incidence of PONV and postoperative fatigue. However, the results for blood loss and transfusion requirements are similar, without increasing the risk of wound infection and gastrointestinal bleeding.

Previous studies have confirmed that local and systemic inflammatory responses are closely related to early postoperative rehabilitation and complications[28–31]. In this study, 20 mg dose of dexamethasone was administered intravenously prior to surgery, which significantly reduced postoperative levels of CRP and IL-6. Our results are consistent with those of previous studies[20,24]. It has been shown to effectively reduce the inflammatory response and pain, thereby accelerating the rapid recovery of patients. Fan and colleagues[32] conducted a systematic review and meta-analysis of dexamethasone in primary total knee arthroplasty, which

TABLE 4 Complications

Parameter	TXA group	TXA + DEX group	*P*
DVT (*n*)	0	0	-
PE (*n*)	0	0	-
Wound superficial infection (*n*)	1	2	1.00
Wound deep infection (*n*)	0	0	-
Gastrointestinal bleeding (*n*)	0	0	-

DEX, dexamethasone; DVT, deep vein thrombosis; PE, pulmonary embolism; *n*, number; TXA, tranexamic acid.; *P* value was analyzed by the Fisher's exact test.

involved eight clinical trials of 1025 patients. The results showed that CPR at 24 h in the dexamethasone group was significantly lower than that in the control group (*SMD* = −0.69, 95% *CI*: 1.15 to −0.23, *P* = 0.003). Similarly, as an anti-fibrinolytic agent, TXA has also been reported to have anti-inflammatory reactions[6,17]. In our study, unlike most studies on the administration of either TXA or DEX, we hypothesized that the combination of TXA and DEX had synergistic and additional benefits in reducing postoperative inflammatory response compared with TXA alone in primary unilateral THA. Our results also confirm the hypothesis that the combined application strategy achieves lower CRP and IL-6 levels.

Previous studies have reported that glucocorticoids can effectively alleviate postoperative pain in THA. Backes *et al.*[33] confirmed that patients receiving dexamethasone experienced more effective pain reduction after THA than in the placebo group. Therefore, the TXA + DEX treatment provides potentially more effective analgesic effects for patients after THA compared to the TXA treatment alone. However, previous studies have confirmed that TXA has anti-inflammatory effects and provides pain relief. It is worth noting that some patients still have symptoms of pain after surgery. As previously reported, the results of the analgesic effect of glucocorticoids are achieved by inhibiting phospholipases, thereby blocking the pathways of cyclooxygenase and lipoxygenase in the inflammatory chain reaction[34]. In addition, it can inhibit the level of bradykinin[35] in tissues and release neuropeptides from nerve endings, reducing tissue inflammation and pain[36]. Therefore, the application of dexamethasone during the perioperative period can potentially compensate for the lack of anti-inflammatory effects of TXA, to further alleviate pain and accelerate the recovery of patients. In our study, we found that an additional 20 mg dexamethasone intravenous injection was effective in improving postoperative pain and reduced the consumption of oxycodone and pethidine hydrochloride after THA.

The antiemetic efficacy of dexamethasone has been well elucidated in previous studies, and its underlying mechanism of action plays an effective role by inhibiting prostaglandin synthesis or endogenous opioid release. Koh *et al.*[24] showed that a single injection of low-dose dexamethasone 10 mg reduced inflammation after total joint replacement, relieved postoperative pain, and prevented PONV. Similarly, a study by Lunn *et al.*[28] reported that steroids can reduce the incidence of PONV through central antiemetics. The current study showed that the incidence of PONV in the TXA + DEX group was significantly lower than in the TXA group.

The optimal routes and doses of dexamethasone remain controversial. A range of doses from 10 to 40 mg in primary THA have been established in most studies. However, most studies report that even when low doses of dexamethasone are used, some patients still suffer from pain, fatigue, and PONV. Therefore, assuming that the effect of low-dose dexamethasone still does not meet the anti-inflammatory requirements, another study showed that dexamethasone has a biological half-life of 36–55 h[25], which is most effective. Therefore, it is reasonable to choose a higher dose of 20 mg during its effective biological half-life. Regarding the dose of intravenous TXA, a range of doses from 1 g to 2 g in total joint arthroplasty has been established in some of the literature, and satisfactory clinical results have been achieved with a dose of 15 mg/kg in our joint replacement center. The current study suggests that a combination of strategies can effectively reduce inflammation and pain, although the results for both groups are consistent in terms of blood loss.

Despite the widespread use of dexamethasone in the perioperative period of surgery, and numerous previously published studies, whether dexamethasone increases the risk of adverse reactions remains controversial[18,20,25]. In this study, additional dexamethasone was given preoperatively, and no surgical site infection or gastrointestinal bleeding occurred during the observation period. At the same time, there was no risk of thrombosis in either group. However, large-scale prospective studies are still needed to assess the safety of combined TXA + DEX.

The present study has some limitations. First, a 3-month follow is not sufficient to determine the safety of TXA + DEX, and longer follow up is needed. However, many previous studies have demonstrated the safety of intravenous administration of TXA and dexamethasone in patients with THA. Second, we included 50 patients in each group, and a smaller sample size would weaken the conviction of the study. Third, the optimal combined dose and timing of TXA + DEX remain unclear and require further study.

Conclusion

The combination of TXA + DEX can reduce postoperative inflammatory response, relieve pain, reduce PONV and fatigue, and without increasing the risk of complications compared to TXA alone. Therefore, the present study suggests that the combination of TXA + DEX is an effective and

safe accelerated rehabilitation strategy for patients receiving primary unilateral THA.

Disclosure

The authors declare that they have no competing interests.

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