CLINICAL ARTICLE

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

Yu-zhang An, MM1, Ming-deng Xu, MM1, Yu-cheng An, MM2, Huan Liu, MM3, Ming Zheng, MD, MM1, Dian-ming Jiang, MD1

Department of 1Orthopaedic Surgery and 2Cardiology, The Third Affiliated Hospital of Chongqing Medical University and 3Department of Surgical Inpatient, Cai Jia Hospital, Chongqing, 401120, China

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 complications1-3. At the same time, surgical trauma in THA can cause severe postoperative inflammation reactions4-6, and is often associated with severe postoperative pain and fatigue7,8, increased incidence of postoperative nausea and vomiting (PONV)9,10, limited range of motion (ROM)11, and prolonged hospital stay12. In addition, inadequate perioperative management is directly related to poor clinical outcomes; Dexamethasone; Total hip arthroplasty; Tranexamic acid

Address for correspondence Jiang Dianming, MD, Department of Orthopaedic Surgery, The Third Affiliated Hospital of Chongqing Medical University, Chongqing, China 401120 Tel: +86-13709401627; Email: 931247352@qq.com Received 17 February 2020; accepted 29 February 2020

An Yuzhang and Xu Mingdeng is the co-first author for this study

Orthopaedic Surgery 2020;12:582-588 • DOI: 10.1111/os.12664
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
patient satisfaction and may hinder recovery after surgery for THA. 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, and it has anti-inflammatory effects. Dexamethasone (DEX), with a strong anti-inflammatory effect, has been widely used to reduce inflammatory markers, prevent PONV, and relieve postoperative pain and fatigue in various perioperative periods. 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. 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/m², 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, 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 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., 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 $\chi^2$-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).
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

---

**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  | 3.48 ± 1.16     | 3.56 ± 1.20     | 0.736 |
| rest               |                 |                 |     |
| Pre-VAS scores at  | 5.16 ± 0.79     | 5.28 ± 0.86     | 0.469 |
| walking            |                 |                 |     |

ASA, America anesthesia association; BMI, body mass index; CRP, C-reactive protein; 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 $\chi^2$-test.

---

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

**Fig. 2** The level of CRP in the two groups. Pre-, preoperative, post, postoperative. *$P < 0.001$. TXA, tranexamic acid; DEX, dexamethasone.
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. 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. It has been shown to effectively reduce the inflammatory response and pain, thereby accelerating the rapid recovery of patients. Fan and colleagues conducted a systematic review and meta-analysis of dexamethasone in primary total knee arthroplasty, which

| 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   |

**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   |

**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’s t-test and Pearson χ² test or 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 lipooxygenase in the inflammatory chain reaction$^{26}$. 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.$^{34}$ 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$^{32}$, 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.

References

1. Kostensalo I, Junnila M, Virolainen P, et al. Effect of femoral head size on risk of revision for dislocation after total hip arthroplasty: a population-based analysis of 42,379 primary procedures from the Finnish arthroplasty register. Acta Orthop, 2013, 84: 342–347.

2. Paulsen A, Pedersen AB, Johnsen SP, Riis A, Lucht U, Overgaard S. Effect of hydroxyapatite coating on risk of revision after primary total hip arthroplasty in younger patients - findings from the Danish hip arthroplasty registry. Acta Orthop, 2007, 78: 622–628.

3. Soo H, Premkumar A, Sheth NP. Projected volume of primary total joint arthroplasty in the US, 2014 to 2030. J Bone Joint Surg Am, 2018, 100: 1455–1460.

4. Miller RA, Ro JY, Schwartz MR. Adverse tissue reactions after total hip arthroplasty. Ann Diagn Pathol, 2017, 28: 141–145.

5. Grant AL, Letson HL, Morris JL, et al. Tranexamic acid is associated with selective increase in inflammatory markers following total knee arthroplasty (TKA): a pilot study. J Orth Surg Res, 2018, 13: 149.

6. Xie J, Hu Q, Ma J, Huang Q, Pei F. Multiple boluses of intravenous tranexamic acid to reduce hidden blood loss and the inflammatory response following enhanced-recovery primary total hip arthroplasty: a randomised clinical trial. Bone Joint J, 2017, 99: B142–B149.

7. Jelski AJ, Deakin AH, Allen DJ, Granat MH, Grant M, Stansfeld BW. Total hip arthroplasty improves pain and function but not physical activity. J Arthroplasty, 2017, 32: 2191–2198.

8. Foucher KC, Cinnamon CC, Ryan CA, Chmell SJ, Dapitton K. Hip abductor strength and fatigue are associated with activity levels more than 1 year after total hip replacement. J Orthop Res, 2018, 36: 1519–1525.

9. Dissanayake R, Du HN, Robertson LK, Ogden K, Willskshire K, Mufford 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: 3429–3436.

10. Nurok M, Cheng J, Romeo GR, Vecino SM, Fields KG, YaDeau JT. Preoperative dexamethasone on the magnitude of the postoperative systemic inflammatory response: a randomized controlled trial. J Bone Joint Surg Am, 2018, 100: 295–304.

11. Zeng WN, Liu JL, Wang FY, Chen C, Zhou Q, Yang L. Low-dose epinephrine plus tranexamic acid reduces early postoperative blood loss and inflammatory response: a randomized controlled trial. J Bone Joint Surg Am, 2018, 100: 295–304.

12. McSorley ST, Roxburgh CSD, Horgan PG, McMillan DC. The impact of preoperative dexamethasone on the magnitude of the postoperative systemic inflammatory response and complications following surgery for colorectal cancer. Ann Surg Oncol, 2017, 24: 2104–2112.

13. Abdelmalak B, Maheshwari A, Mascha E, et al. Design and organization of the dexamethasone, light anesthesia and tight glucose control (DeLiT) trial: a factorial trial evaluating the effects of corticosteroids, glucose control, and depth-of-anesthesia on perioperative inflammation and morbidity from major non-cardiac surgery. BMC Anesthesiol, 2010, 10: 11.

14. Lei Y, Huang Q, Xu B, Zhang SY, Cao GR, Pei FX. Multiple low-dose perioperative dexamethasone further reduces blood loss following total hip arthroplasty. J Arthroplasty, 2018, 33: 1426–1431.

15. Xu B, Ma J, Huang Q, Huang YZ, 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 Arthrosoc, 2018, 26: 1549–1556.

16. Parthasarathy P, Babu K, Raghavendra Rao RS, Raghuram S. The effect of single-dose intravenous dexamethasone on postoperative pain and postoperative nausea and vomiting in patients undergoing surgery under spinal Anaesthesia: a double-blind randomized clinical study. Anesth Essays Res, 2018, 12: 313–317.

17. Fan ZR, Ma JX, Ma XL, et al. The efficacy of dexamethasone on pain and recovery after total hip arthroplasty: a systematic review and meta-analysis of randomized controlled trials. Medicine, 2018, 97: e100017.

18. Koh LJ, 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: 3010–3020.

19. Samona J, Cook C, Kuppa K, et al. Effect of intraoperative dexamethasone on pain scores and narcotic consumption in patients undergoing total knee arthroplasty. Orthop Surg, 2017, 9: 110–114.

20. Lynn M, Maclachlan L, Finkelmanevey, et al. Reduction of glucocorticoid receptor function in chronic fatigue syndrome. Mediat Inflamm, 2016, 2018: 18792104.

21. Yue C, Wei R, Liu YW. 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.

22. Lunn TH, Kristensen BB, Andersen LO, 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: 230–238.

23. Aiazzi W, Pirmajid N, Lahiri R, Bhattacharya S. Inflammatory and immune responses to surgery and their clinical impact. Ann Surg, 2016, 264: 73–80.

24. Xu JD, Qu YX, Gao Y, Zhao H, Deng LB, Zhao JN. Impact of preemptive analgesia on inflammatory responses and rehabilitation after primary total knee arthroplasty: a controlled clinical study. Sci Rep, 2016, 6: 3054.

25. Liu W, Cong RJ, Li XM, Wu YL, Wu HS. Reduced opioid consumption and improved early rehabilitation with local and intraarticular cocktail analgesic injection in Total hip arthroplasty: a randomized controlled clinical trial. Pain Med, 2011, 12: 387–393.

26. Fan ZR, Ma JX, Huang MJ, et al. The efficacy of dexamethasone reducing postoperative pain and emesis after total knee arthroplasty: a systematic review and meta-analysis. Int J Surg, 2018, 52: 149–155.

27. 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: 11–17.

28. Saposilky RM, Romero LM, Munck AU. Do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev, 2000, 21: 55–89.

29. Hargreaves KM, Costello A. Glucocorticoids suppress levels of Immunoreactive bradykinin in Inflamed tissue as evaluated by microdialysis probes. Clin Pharmacol Ther, 1985, 38: 643–652.

30. Hong D, Byers MR, Oswald RJ. Dexamethasone treatment reduces sensory neuropeptides and nerve sprouting reactions in injured teeth. Pain, 1993, 55: 171–181.