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Perioperative combined administration of tranexamic acid and dexamethasone in total knee arthroplasty—benefit versus harm?

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Abstract

Background: The purpose of this study was to investigate the benefits and harm of combined administration of tranexamic acid (TXA) and dexamethasone (Dexa) in total knee arthroplasty (TKA).

Methods: A total of 88 consecutive patients undergoing TKA for knee osteoarthritis were stratified in 2 groups. All surgeries were performed under general anesthesia. Brief, patients in the TXA + Dexa group (n = 45) received 10 mg Dexa just after the anesthesia, and repeated at 24 hours after the surgery; and patients in the TXA group (n = 43) received 2 ml of normal saline solution at the same time. The measured outcomes were the C-reactive protein (CRP) and interleukin-6 (IL-6) from preoperatively to postoperatively, and postoperative nausea and vomiting (PONV), fatigue, range of motion (ROM), length of stay (LOS), and the analgesic and antiemetic rescue consumption

Results: The level of CRP and IL-6 in the TXA + Dexa group were lower than that in the TXA group at 24 hours ($P < .001$, $P < .001$), 48 hours ($P < .001$, $P < .001$), and 72 hours ($P < .001$, $P < .001$) after the surgery. The pain scores in the TXA + Dexa group were lower during walking at 24 hours ($P < .001$), 48 hours ($P < .001$), and 72 hours ($P < .001$) and at rest at 24 hours ($P = .022$) after the surgery. Patients in the TXA + Dexa group had a lower nausea score, the incidence of PONV, fatigue, and the analgesic and antiemetic rescue consumption, and had a greater ROM than that in the TXA group. No significant differences were found in LOS and complications.

Conclusion: The combined administration of TXA + Dexa significantly reduced the level of postoperative CRP and IL-6, relieve postoperative pain, ameliorate the incidence of POVN, provide additional analgesic and antiemetic effects, reduce postoperative fatigue, and improve ROM, without increasing the risk of complications in primary TKA.

Abbreviations: BMI = body mass index, CRP = C-reactive protein, DVT = deep venous thrombosis, IL-6 = interleukin-6, PE = pulmonary embolism, PONV = postoperative nausea and vomiting, ROM = range of motion, TKA = total knee arthroplasty, VAS = visual analog scale.

Keywords: benefit and harm, dexamethasone, total knee arthroplasty

1. Introduction

Total knee arthroplasty (TKA) is an effective treatment for knee osteoarthritis, and many studies have suggested good long-term survivorship as well as better kinematics, lower pain level, and complications in osteoarthritis knee.[1–3] However, the inflammatory response following TKA is obvious and a result of the cumulative effects of anesthesia and surgical stress.[4,5] As previously reported, inflammation is associated with postsurgical pain,[6,7] postoperative nausea and vomiting (PONV),[8,9] fatigue,[10,11] resulting in increased dissatisfaction,[12,13] and impeding functional recovery.[14,15] Therefore, the management of postoperative inflammation will be largely beneficial to the fast-track of TKA patients.

Tranexamic acid (TXA), as an analog of the amino acid lysine, can competitively inhibit plasminogen activation and binding of plasmin to fibrin, thereby inhibiting fibrinolysis.[16–19] A large number of previously published Level I evidence have confirmed that the use of TXA can significantly reduce blood loss and transfusion requirements, and can also effectively inhibit the postoperative inflammatory response and reduce postoperative pain. In addition, a multimodal analgesia regime is also required to reduce the postoperative inflammatory response and to relieve pain. Dexamethasone (Dexa), which has strong anti-inflammatory effects,[20,21] is widely used in various perioperative management in reducing the inflammatory response, preventing POVN, relieving postoperative pain and fatigue.[4,7,11,21,22] Although the majority of studies involving glucocorticoid in the setting of TKA have focused on the intravenous[11,23,24] and articular injection[25–27] of administration routes, to our knowledge, investigating the association of glucocorticoids and

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All data and materials are contained within the manuscript.

The study was approved by the Institutional Review Board of No. 2 People's Hospital of Yibin City, Sichuan Province. All participants must provide written informed consent to participate.

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TXA in TKA was less reported. Furthermore, also to our knowledge, there have been no prospective studies comparing the combined application of TXA + Dexa in TKA, and the benefits and clinical outcomes in TKA treatment are unclear.

Thus, we performed a randomized, controlled trial to compare the efficacy of TXA + Dexa in TKA. We hypothesized that,

(1) whether the combined application of TXA + Dexa reduces the level of postoperative inflammatory response, including C-reactive protein (CRP) and interleukin-6 (IL-6);
(2) whether the combined application of TXA + Dexa reduces postoperative pain, PONV, and fatigue;
(3) whether the combined application of TXA + Dexa have additional analgesic and antiemetic effects;
(4) whether the combined application of TXA + Dexa improves the range of motion and increases the risk of postoperative complications.

2. Material and methods

2.1. Study design and patients

The study was approved by the Institutional Review Board of No. 2 People's Hospital of Yibin City of Sichuan Province, and the Research Registration Unique Identifying Number (research registry 4657). Written informed consent was received from each patient. Patients with a diagnosis of the osteoarthritis following primary TKA were eligible for inclusion. Revision TKA, infection, allergy to the Dexa, administration of glucocorticoid 3 months before the operation, history of severe heart disease (New York Heart Association >2), knee flexion less than 90° were excluded. A total of 90 patients were randomly assigned to each group: the TXA group and the TXA + Dexa group. A random number table concealed at a ratio of 1:1 was computer-generated by a nurse. Randomization was blind and performed with the use of sealed envelopes before the surgery by a nurse. Briefly, all patients in the TXA + Dexa group were taken 15 mg/kg TXA 10 minutes before the incision, and repeated 1 g TXA 3 hours after surgery, and all patients received intravenously 10 mg Dexa (2 ml, Tianjin Kingyork group Co, Ltd, China) just after the anesthesia, and repeated at 24 hours after the surgery, and patients in the TXA group were taken 15 mg/kg TXA 10 minutes before the incision, and repeated 1 g TXA 3 hours after surgery. To support the double-blind study, all patients received intravenously 2 ml of the normal saline solution just after the anesthesia and repeated at 24 hours after the surgery.

2.2. Surgery, anesthesia, and postoperative care

All TKAs were performed by a similar orthopedic surgeon, and all of the TKAs were performed using a midline skin incision, medial parapatellar approach. The cemented, posterior-stabilized prosthetic design without patellar resurfacing was used for all patients. All surgery was performed under general anesthesia. There was no nerve block or patient-controlled intravenous analgesia during the perioperative period. All patients were subcutaneously injected with low molecular weight heparin at 6 hours after operation after the surgery. Deep venous thrombosis (DVT) was evaluated at the time of discharge and 3 months after operation using Doppler ultrasound. At the end of the surgery, the pain levels were assessed using a visual analog scale (VAS, 0 – no pain, 10 – worst imaginable pain). Oral oxycodone 10 mg q8h was used if the VAS level is between 4 and 6. An intramuscular injection of pethidine hydrochloride 100 mg was used if the patient indicated the pain level more than 6. Nausea was assessed using VAS (VAS, 0 – on nausea, 10 – worst imaginable nausea). Patients received metoclopramide 10 mg as the first-line antiemetic rescue if PONV is more than 2 times. Ondansetron 5 mg was used as the second-line antiemetic rescue if nausea still occurred after 2 doses of metoclopramide for 30 minutes interval. The total blood loss was assessed by the Gross formula, and blood transfusion was referenced by the Chinese Ministry of Health, with a Hb level of <70 g/L or 70–100 g/L, or symptoms of anemia (such as mental state and dizziness, etc).

2.3. Outcome measurements

CRP, IL-6, VAS pain scores at rest and walking, the VAS scores of nausea, and the incidence of POVN were recorded at 24, 48 and 72 hours postoperatively. Nausea is defined as a subjective sensation associated with the impulse to be conscious of vomiting. Vomiting is the forcible discharge of stomach contents from the mouth.

The total number and dosage of patients requiring analgesic drugs (Oxycodone and Pethidine hydrochloride) were recorded postoperatively. The total number and dosage of patients requiring antiemetic rescue drugs (Metoclopramide and Ondansetron) were also recorded postoperatively.

Fatigue was assessed using a 10-point numeric rating scales (NRS, 1- fit, 10-fatigued)[28] before surgery and at the time of discharge. Range of motion (ROM) was assessed before surgery and at the time of discharge by a nurse using a goniometer. The length of stay (LOS) and complications were recorded carefully.

2.4. Statistical analysis

The sample size was calculated, as previously described by Rytter et al,[27] using VAS level score as the primary outcome; it was determined that, for 90% power and a significance level of 0.05, requiring 41 patients in each group. Therefore, we decided to include 45 patients in each group in the study, assuming a 10% loss to follow-up.

Continuous variables were calculated as by Student *t* test (which were presented as mean ± standard deviation), such as CRP, IL-6, VAS pain scores at rest and walking, VAS scores of nausea, fatigue scores, ROM, and LOS. The Pearson chi-square test or Fisher exact test was used to comparing qualitative data, such as the incidence of PONV, and complications. Statistical analyses were conducted using SPSS for windows, version22.0 (SPSS Inc, Chicago, IL). $P < .05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

During the recruitment period, 96 patients with osteoarthritis for primary unilateral TKA. Six were ineligible for inclusion, 2 patients with glucocorticoid 3 months before surgery, 1 had alcohol dependence, 3 declined to participate. Thus, the remaining 90 patients were enrolled in the study and all completed follow-up (mean 3 months, 2–4); however, 2 patients lost follow-up in the TXA group. Thus, 45 patients were assigned to the TXA + Dexa group and 43 patients were assigned to the TXA group (Fig. 1). Baseline characteristics were summarized in Table 1, no differences were found in both groups.

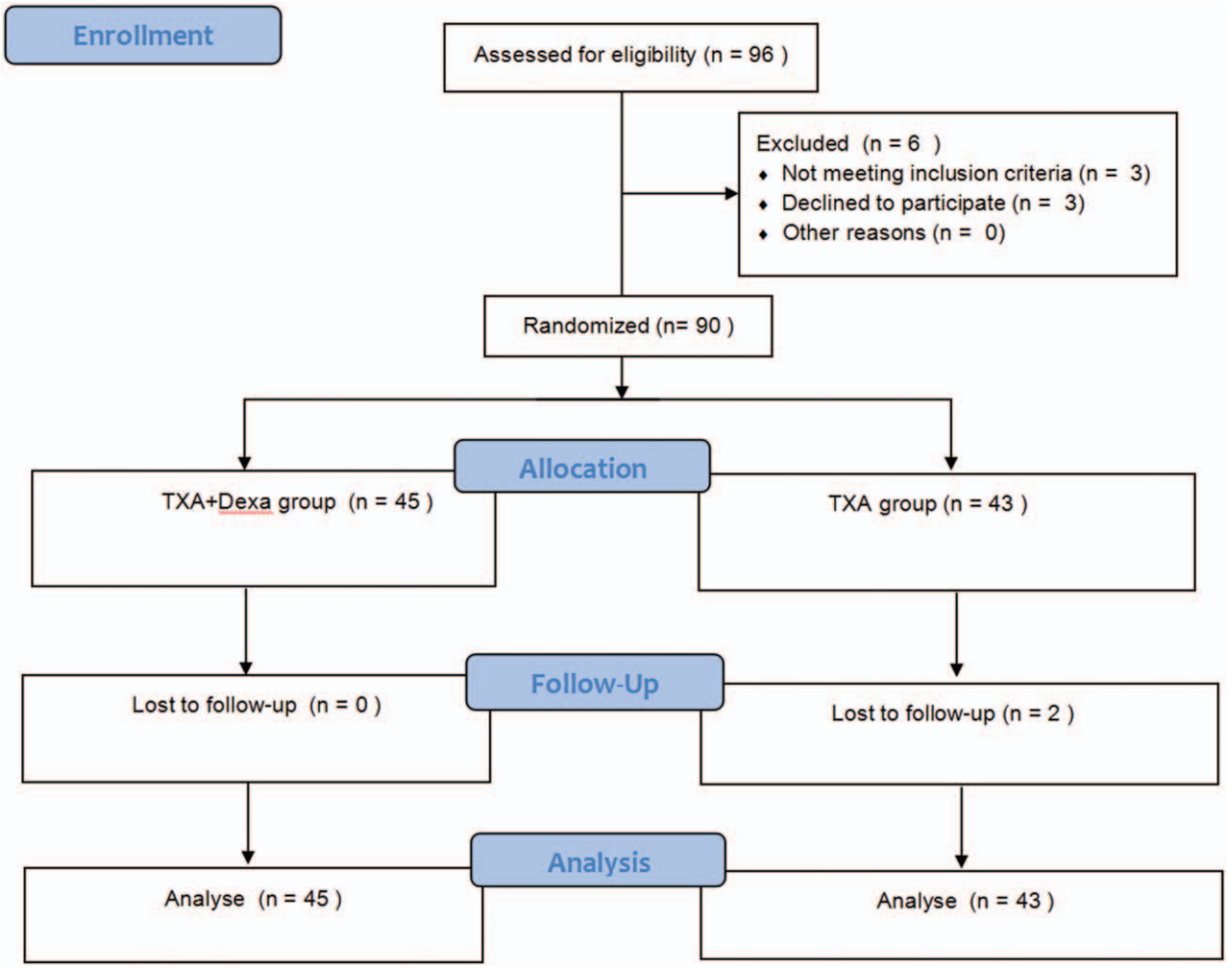

Figure 1. A flow diagram shows the study design.

Table 1

Baseline characteristics.

Variable	TXA group (n = 43)	TXA + Dexa group (n = 45)	*P*-value
Age, yr*	64.18 ± 3.40	65.05 ± 3.44	.256
Gender (M/F) (n)†	17/26	19/26	.798
Height, cm*	159.60 ± 6.94	158.50 ± 5.31	.428
Weight, kg*	66.15 ± 4.90	65.98 ± 3.74	.858
BMI, kg/m^2*	26.04 ± 2.24	26.31 ± 1.89	.559
Operated site, R/L†	24/19	25/20	.981
ASA scores*	1.88 ± 0.65	1.90 ± 0.67	.866
Hypertension (n)†	5	7	.591
Type 2 diabetes (n)†	8	7	.704
Preop. Hb, g/dL*	13.37 ± 0.57	13.40 ± 0.55	.764
Preop. Hct, L/L*	39.70 ± 1.25	39.78 ± 1.28	.772
Preop. CRP, mg/L*	3.21 ± 0.78	3.30 ± 0.94	.650
Preop. IL-6, pg/mL*	3.86 ± 1.20	3.91 ± 0.67	.830
Preop. ROM, °*	93.13 ± 1.79	94.78 ± 2.89	.483
Preop. Pain at walking (0–10)*	5.15 ± 0.70	5.18 ± 0.75	.878
Preop. Pain at rest (0–10)*	3.83 ± 0.71	3.90 ± 0.90	.681
Preop. Fatigue (0–10)*	4.10 ± 0.87	4.28 ± 0.93	.389
Operation time, min*	66.29 ± 3.59	67.40 ± 3.73	.123

P-value indicates a significant difference in both groups.

ASA = American Society of Anesthesiologists, BMI = body mass index, CRP = C-reactive protein, Dexa = dexamethasone, F = female, Hb = hemoglobin, Hct = hematocrit, IL-6 = interleukin-6, L = left, M = male, n = number, Preop = preoperative, R = right, ROM = range of motion, TXA = tranexamic acid.

* Analyzed by the Student *t* test.

† Analyzed by the Pearson chi-square test or the Fisher exact test.

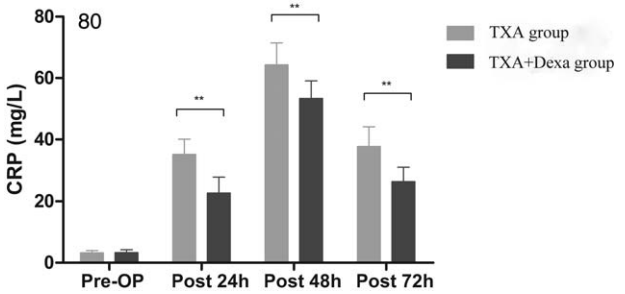

Figure 2. A graph shows the level of CRP in both groups. The results indicate that it was lower in the TXA + Dexa group than that in the TXA group at 24 h, 48 h, and 72 h after the surgery. ** indicates $P < .001$. CRP = C-reactive protein, Dexa = dexamethasone, Pre-OP = preoperative, Post = postoperative, TXA = tranexamic acid.

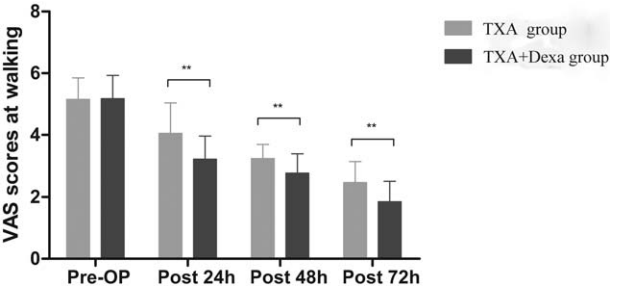

Figure 4. A graph shows the level of pain at walking in both groups. The results indicate that it was lower in the TXA + Dexa group than that in the TXA group at 24 h, 48 h, and 72 h after the surgery. ** indicates $P < .001$. Dexa = dexamethasone, Pre-OP = preoperative, Post = postoperative, TXA = tranexamic acid.

3.2. CRP and IL-6

In all patients, acute inflammatory markers CRP and IL-6 increased after the surgery. The average level of CRP in both groups reached a peak at 48 hours after the surgery, and it was lower in the TXA + Dexa group than that in the TXA group at 24 ($P < .001$), 48 ($P < .001$), and 72 hours after the surgery ($P < .001$) (Fig. 2).

The average level of IL-6 in the TXA group reached a peak at 24 hours after the surgery; however, it reached a peak in the TXA + Dexa group at 48 hours after the surgery. Similarly, it was lower in the TXA + Dexa group than that in the TXA group at 24 ($P < .001$), 48 ($P < .001$), and 72 hours after the surgery ($P < .001$) (Fig. 3).

3.3. Pain and rescue analgesic requirement

The postoperative VAS scores in both groups were significantly lower in the TXA + Dexa group than those of the TXA group for all 2 pain assessments. Time-specific pain scores were lower during walking at 24 hours ($P = .004$), 48 hours ($P = .004$), and 72 hours ($P = .004$) after the surgery, and at rest at 24 hours ($P = .004$) after the surgery (Figs. 4 and 5).

Six patients in the TXA + Dexa group required less oxycodone than 19 patients in the TXA group ($P = .001$), and the cumulative consumption of oxycodone was also significantly lower in the TXA + Dexa group ($P < .001$). Compared with the TXA group, the number of patients requiring pethidine hydrochloride did not differ between the groups during the remaining study period ($P = .113$); however, the cumulative consumption was also lower in the TXA + Dexa group ($P = .041$) (Table 2).

3.4. PONV and antiemetic requirement

The postoperative VAS scores for nausea in both groups were significantly lower in the TXA + Dexa group than those of the TXA group. Time-specific nausea scores were lower at 24 hours ($P = .001$), 48 hours ($P = .014$), and 72 hours ($P = .015$) after the surgery. The incidence of PONV was generally lower in the study than that in the TXA group at 24 hours ($P = .036$), 48 hours ($P = .032$), and 72 hours ($P = .013$) after the surgery (Table 3).

Compared with the TXA group, the number of patients requiring metoclopramide in the TXA + Dexa group was significantly fewer ($P = .002$), and the cumulative consumption of metoclopramide was also significantly lower. The number of patients requiring ondansetron was no difference in both groups ($P = .006$). However, the cumulative consumption of ondansetron in the study was less ($P = .320$) (Table 2).

3.5. Fatigue, ROM, LOS, and blood loss

Fatigue was significantly lower in the TXA + Dexa group compared with the TXA group at the time of discharge

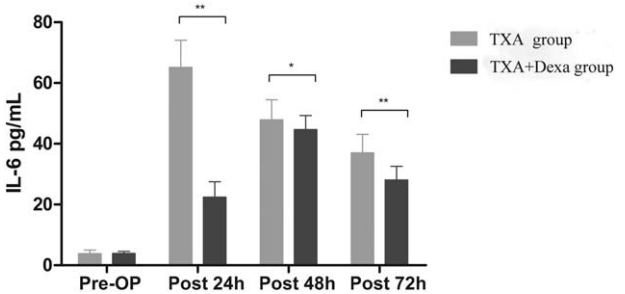

Figure 3. A graph shows the level of IL-6 in both groups. The results indicate that it was lower in the TXA + Dexa group than that in the TXA group at 24 h, 48 h, and 72 h after the surgery. * indicates $P < .05$; ** indicates $P < .001$. Dexa = dexamethasone, IL-6 = interleukin-6, Pre-OP = preoperative, Post = postoperative, TXA = tranexamic acid.

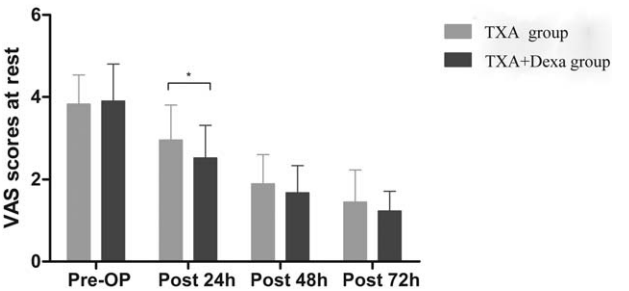

Figure 5. A graph shows the level of pain at the rest in both groups. The results indicate that it was lower in the TXA + Dexa group than that in the TXA group at 24 h after the surgery. * indicates $P < .05$. Dexa = dexamethasone, Pre-OP = preoperative, Post = postoperative, TXA = tranexamic acid.

Table 2

The total requirement of rescue analgesic and antiemetic in both groups.

Variables	TXA group (n = 43)	TXA + Dexa group (n = 45)	*P*-value
Oxycodone			
Number of patients requiring (n)†	19	6	.001
Cumulative consumption, mg*	880	140	<.001
Pethidine hydrochloride			
Number of patients requiring (n)†	4	0	.113
Cumulative consumption, mg*	400	0	.041
Metoclopramide			
Number of patients requiring (n)†	18	5	.002
Cumulative consumption, mg*	260	30	.006
Ondansetron			
Number of patients requiring (n)†	4	0	.114
Cumulative consumption (mg)*	10	0	.320

P-value indicates a significant difference in both groups.
Dexa = dexamethasone, n = number, TXA = tranexamic acid.
* Analyzed by the Student *t* test.
† Analyzed by the Pearson chi-square test or the Fisher exact test.

Table 3

The clinical outcomes in both groups.

Variables	TXA group (n = 43)	TXA + Dexa group (n = 45)	*P*-value
Intensity of Nausea-post 24 h*	2.68 ± 1.12	1.73 ± 1.22	.001
Intensity of Nausea-post 48 h*	1.50 ± 0.68	1.08 ± 0.83	.014
Intensity of Nausea-post 72 h*	1.10 ± 0.81	0.65 ± 0.80	.015
PONV-post 24 h†	19	10	.036
PONV-post 48 h†	13	5	.032
PONV-post 72 h†	8	1	.013
Fatigue scores*	6.83 ± 1.03	5.65 ± 0.92	<.001
ROM*	101.15 ± 2.41	103.63 ± 1.88	<.001
LOS, d*	4.58 ± 0.90	4.28 ± 0.68	.097
Total blood loss, mL	958.4 ± 278.2	948.2 ± 298.1	.358
Transfusion rates (n)	5	4	.943

P-value indicates a significant difference in both groups.
Dexa = dexamethasone, h = hours, LOS = length of stay, Post = postoperative, POVN = postoperative nausea and vomiting, ROM = range of motion, TXA = tranexamic acid.
* Analyzed by the Student *t* test.
† Analyzed by the Pearson chi-square test or the Fisher exact test.

($P < .001$). Patients in the TXA + Dexa group had a greater ROM than that in the TXA group at the time of discharge, it was statistically significant in both groups. The average LOS in the TXA + Dexa and TXA group were 4.28 ± 0.68 and 4.58 ± 0.90 days, respectively, there was no difference in both groups. No difference in blood loss and transfusion rate.

3.6. Complications

No patient had DVT and PE. One patient in the TXA + Dexa group was readmitted 1 month after the surgery due to superficial wound infection, which was controlled by antibiotics and dressing change. No other complications or side effects were recorded (Table 4).

Table 4

Complications in both groups.

Variables	TXA group (n = 43)	TXA + Dexa group (n = 45)	*P*-value
DVT (n)*	0	0	–
PE (n)*	0	0	–
Deep infection (n) *	0	0	–
Superficial infection (n)*	0	1	1
Gastrointestinal hemorrhage (n)*	0	0	–

P-value indicates a significant difference in both groups.
Dexa = dexamethasone, DVT = deep vein thrombosis, N = number, PE = pulmonary embolism, TXA = tranexamic acid.
* Analyzed by the Pearson chi-square test or the Fisher exact test.

4. Discussion

The administration of glucocorticoid seems to be well applied in lower limb arthroplasty for anti-inflammatory response and pain relief.[4,11,24,27,29,30] However, as far as we know, this is only the first study on the combined administration of TXA + Dexa in TKA, although this is limited to some extent by small samples. The important findings of this study confirm the hypothesis that the combined application pf TXA + Dexa can significantly reduce postoperative CRP and IL-6 levels, relieve postoperative pain, PONV, and fatigue, provide additional analgesia and antiemetic effects, improve the knee ROM, without increasing the risk of postoperative complications.

As acute inflammatory markers, levels of CRP and IL-6 have similar dynamic changes during inflammation.[31] The anti-inflammatory effect of glucocorticoid is associated with the pathway of prostaglandin and cyclo-oxygenase, which acts directly on nuclear steroid receptors and controls the synthesis rate of mRNA and protein.[32] Consequently, the activity of phospholipase A2 was inhibited,[33] resulting in the reduction of arachidonic acid proinflammatory derivatives. In addition, the use of TXA in TKA has been well established, whether it is intravenous,[16,19] topical,[17,18] or combined administration.[34,35] Although, the optimal dose, treatment time, and route of administration of TXA are still controversial. Xie et al[16] conducted a randomized controlled trial of 151 patients receiving primary TKA who received a single bolus of 20 mg/kg intravenous TXA, another bolus of 10 mg/kg intravenous TXA 3 hours later or another 2 boluses of 10 mg/kg intravenous TXA 3 hours and 6 hours later. The results showed that multiple boluses of intravenous TXA can effectively reduce postoperative inflammatory response and pain after primary TKA without a tourniquet. In the present study, the combination of Dexa and TXA further significantly reduced CRP and IL-6 levels at 24, 48, and 72 hours after surgery, reducing postoperative pain and accelerating rapid recovery.

The postoperative pain in TKA can be caused by the trauma to the soft tissue or osteotomy. Analgesic effect of glucocorticoid after knee arthroplasty has been well confirmed; however, the analgesic effect and opioid requirement were inconsistent. Pang et al[25] suggested patients received 40 mg periarticular steroid injection had a significant reduction in pain at 12, 18, 24 hours postoperatively compare with the patients without steroid injection after TKA. Koh et al[30] reported that preoperative administration of a single dose of 10 mg Dexa in TKA reduced postoperative pain during the 6 to 24 hours, and it also reduced opioid consumption during the full 72 hours after the surgery. Lunn et al[11] indicated that a sing dose of 125 mg methylprednisolone in TKA reduced pain for the first 48 hours after surgery. However, there was no study have evaluated the effect of TXA + Dexa for pain relief in primary TKA. In our study, the pain score was lower in the study during walking at 24, 48, 72 hours and during rest at 24 hours after the surgery, and the consumption of oxycodone and pethidine hydrochloride was less. There are several possible reasons underlying the analgesic effects observed in the TXA + Dexa group. First, glucocorticoids can inhibit phospholipase, therefore, blocking the cyclooxygenase and lipoxygenase pathway in the inflammatory chain reaction and achieving an analgesic effect.[36] Second, as previously reported, the most significant postoperative pain after TKA was at 48 hours postoperatively; however, the maximum analgesic effect of a single dose of Dexa was at 24 hours postoperatively in most studies.[4,11,24,25] Therefore, an additional dose of Dexa 24 hours after surgery may provide potentially additional analgesic effects. The results indicate that the 2 doses of Dexa to further reduce the pain of short-term efficacy compared to the TXA group. It is worth noting that it has not been proven whether the management of glucocorticoids can reduce the long-term consequences of pain.

Dexa can potentially reduce the incidence of vomiting by modulating prostaglandin synthesis or inhibiting endogenous opioid release.[37] In present studies,[4,11,25,27] it has been well established to support and recommendation for the use of a single dose glucocorticosteroid reducing the incidence of PONV. Compared to the single-dose route, we hypothesized that patients would receive further POVN remission to supplement additional dose 24 hours after surgery. In our study, the TXA + Dexa group had lower VAS scores for nausea and incidence of PONV, and the consumption of metoclopramide was less, although the requirements for ondansetron were similar in both groups.

Although Dexa is widely used in the perioperative period of knee arthroplasty. However, previous literature still remains controversial as to whether Dexa increases the risk of adverse reactions. In the present study, 2 doses of low-dose perioperative Dexa were administrated in TKA, and 1 patient developed superficial infections during follow-up, but no other severe side effects occurred. In addition, our findings have been supported by published studies in recent years.[4,11,24,29] Generally, the administration of Dexa does not increase the risk of adverse reactions.

The study has several limitations. First, the follow-up evaluation did not assess long-term clinical outcomes, such as pain VAS scores and functional improvement. Second, our postoperative analgesia and antiemetic regimens include extensive multimodal pain management and methods, such as prevention of intra-articular injections of ropivacaine, celecoxib, pregabalin, oxycodone and pethidine hydrochloride, metoclopramide and ondansetron. The important reason is to consider the perioperative multi-mode fast-track rehabilitation strategy in our joint center, however, whether there is synergy or antagonism between these drugs, and whether the effects of Dexa will be affected, which requires further study. Third, the study administrated only 2 doses of Dexa is a limitation, and further work should explore the efficacy and safety of other doses. Fourth, although this sample size was calculated through present studies, showing the result of sufficient sample size in the follow-up of complications, and the results indicated that the incidence of complications was lower in the present study. However, more high-quality, large-sample, prospective trials were required to further confirm whether multiple doses of Dexa is associated with an increased risk of side effects in patients undergoing TKA. Last, all patients received bone cement prostheses in the study; however, bone cement, in particular, is a hypotensive agent that can also potentially cause nausea, which requires further confirmation of whether different types of prostheses have an effect on the incidence of nausea.

5. Conclusions

The combined administration of TXA + Dexa significantly reduced the level of postoperative CRP and IL-6, relieve postoperative pain, ameliorate the incidence of POVN, provide additional analgesic and antiemetic effects, reduce postoperative

fatigue, and improve ROM without increasing the risk of complications in primary TKA.

Author contributions

Conceptualization: You Yu.
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Formal analysis: Hai Lin.
Investigation: Hai Lin, Zhitao Wu.
Methodology: You Yu, Zhengliang Lei.
Project administration: Peng Xu.
Resources: Zhitao Wu.
Software: You Yu, Hai Lin, Peng Xu.
Supervision: Peng Xu.
Validation: Zhitao Wu.
Visualization: Zhitao Wu.
Writing – original draft: You Yu.
Writing – review and editing: You Yu.

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