CLINICAL ARTICLE

Combination of Intravenous and Intra-Articular Application of Tranexamic Acid and Epsilon-Aminocaproic Acid in Primary Total Knee Arthroplasty: A Prospective Randomized Controlled Trial

Che Zheng, MD, Jun Ma, MD, Jiawen Xu, MD, Haibo Si, MD, Yuan Liu, MD, Mingyang Li, MD, Bin Shen, MD

Department of Orthopaedics, West China Hospital, Sichuan University, Chengdu, China

Objective: There were limited randomized controlled trials (RCTs) of epsilon-aminocaproic acid (EACA) versus tranexamic acid (TXA) in total knee arthroplasty (TKA). The aim of the study was to compare the efficacy and safety of TXA and EACA in the combination of intravenous (IV) and intra-articular (IA) administration on reducing blood loss in patients following primary TKA.

Methods: From January 2020 to January 2021, a total of 181 patients undergoing a primary unilateral TKA were enrolled in this prospective randomized controlled trial. Patients in the TXA group ($n = 90$) received 20 mg/kg of intravenous TXA preoperatively, 1 g of intra-articular TXA intraoperatively, and three doses of 20 mg/kg intravenous TXA at 0, 3, 6 h postoperatively. Patients in the EACA group ($n = 91$) received 120 mg/kg of intravenous EACA preoperatively, 2 g of intra-articular EACA intraoperatively, and three doses of 40 mg/kg intravenous EACA at 0, 3, 6 h postoperatively. The primary outcomes were total blood loss (TBL), transfusion rates and drop of hemoglobin (HB) level. The secondary outcomes included postoperative hospital stays and postoperative complications. The chi-square tests and Fisher's exact tests were utilized to compare categorical variables, while the independent-samples *t*-tests and Mann–Whitney tests were used to compare continuous variables.

Results: The patients who received TXA averaged less TBL than the patients who received EACA (831.83 ml *vs* 1065.49 ml, $P = 0.015$), and HB drop in TXA group was generally less than that of EACA group on postoperative day 1 and 3 (20.84 ± 9.48 g/L *vs* 24.99 ± 9.40 g/L, $P = 0.004$; 31.28 ± 11.19 *vs* 35.46 ± 12.26 g/L, $P = 0.047$). The length of postoperative stays in EACA group was 3.66 ± 0.81 day, which is longer than 2.62 ± 0.68 day in TXA group ($P < 0.001$). No transfusions were required in either group. The risk of nausea and vomiting in TXA group was significantly higher than that in EACA group (11/90 *vs* 0/91, $P < 0.01$).

Conclusion: Although the TBL and HB drop were slightly greater in EACA group, these results were not clinically important, given that no transfusions were required. EACA could be an alternative to TXA, especially for patients with severe nausea and vomiting after using TXA postoperatively. Further studies are needed to adjust dosage of EACA to make better comparison of the two drugs.

Key words: Total knee arthroplasty; Tranexamic Acid; Epsilon-aminocaproic acid; Bleeding

Address for correspondence Bin Shen, Department of Orthopaedics, West China Hospital, Sichuan University, 37# Guoxue Road, Chengdu, 610041, China. Tel: +86-13881878767; Fax: +86-028-85423438; Email: shenbin_1971@163.com
Che Zheng and Jun Ma Co-first authors.
Received 14 September 2022; accepted 27 November 2022

Introduction

Total knee arthroplasty (TKA), which was estimated to grow by 85% to 1.26 million in 2030,[1] is the major surgical procedure to alleviate pain and improve knee function for patients suffering from end-stage arthrosis of the knee.[2,3] However, patients who had TKA may lose a lot of blood after the surgery, which may require a large amount of blood transfusion.[4] Blood transfusion not only costs a great deal of manpower and material resources, but also had many adverse clinical risks, including infection, intravascular hemolysis, kidney damage, immune incompatibility, and even death.[5,6] Meanwhile, massive bleeding in the knee cavity and soft tissue space will aggravate the swelling and pain, adversely affecting patients' willingness for postoperative rehabilitation exercise and the overall satisfaction of the operation.[7]

Hyperfibrinolysis following surgery was a major cause for perioperative blood loss in TKA.[8] As an antifibrinolytic agent, tranexamic acid (TXA) has been widely used to control bleeding for patients undergoing a joint replacement. The effect of TXA on reducing blood loss and transfusion rates has been well-demonstrated in joint surgeries over the past several decades.[9,10] However, antifibrinolytic agents have a potential effect on increasing risk for deep vein thrombosis (DVT) and pulmonary embolism (PE). In addition, TXA was commonly used as an emetic for animals.[11,12] Severe nausea and vomiting have been reported in patients after intravenous administration of TXA in several studies,[13,14] which can lead to a marked increase of morbidity and mortality in critically ill patients due to major complications, such as aspiration pneumonia, esophagitis, and esophageal stricture. Epsilon-aminocaproic acid (EACA) shared similar mechanism actions with TXA, both of them saturate the lysine binding sites of plasminogen. However, their potencies for saturating lysine binding sites are different.[15,16] Unlike TXA, the effect of EACA was mainly focused on cardiac surgeries.[17–19] The efficacy of EACA on blood loss reduction in total joint surgery remains to be investigated in more detail.

Antifibrinolytic agents could be administrated intravenously, intra-articularly, orally or combined. Though several studies have compared the efficacy of TXA and EACA in total joint replacement surgery, none of them compared the two drugs when the drugs were administered in an intravenous and intra-articular (IV/IA) combined fashion.[20–22] IV/IA combined administration has become more and more common recently in TKA as it can reduce both apparent and hidden blood loss.[23,24] However, the optimal regimen of antifibrinolytic agents, as well as efficacy of EACA and TXA, are still controversial in TKA.

Based on this, we conducted a double-blinded prospective randomized controlled trial and aimed to investigate the following: (i) could EACA be an alternative to TXA in reducing bleeding in the IV/IA combined application?; and (ii) were there any significant differences in postoperative complications such as severe nausea and vomiting between EACA and TXA groups?

Materials and Methods

Study Design

This double-blinded prospective randomized controlled trial was registered in the Chinese Clinical Trial Registry (ChiCTR2000032271). Patients scheduled for primary unilateral TKA from January 2020 to January 2021 were enrolled in this study. All the participants signed the written consent forms. This study was approved by the clinical trials and biomedical ethics committee, West China Hospital, Sichuan University (No: 2012–268).

Enrollment and Screening

All patients who were 40 years older and scheduled for a primary unilateral TKA for end-stage osteoarthritis were eligible for this study. Exclusion criteria included: (i) patients with surgery other than primary unilateral total knee arthroplasty, such as revision and bilateral total knee replacement; (ii) preoperative anemia (HB level < 110 g/L; history of erythropoietin (EPO), iron supplements and folic acid administration); and coagulation disorders (preoperative D-Dimer > 3 times normal level; prolonged PT, APTT or INR; history or preoperative condition of deep vein thrombosis (DVT), pulmonary embolism (PE) or intramuscular venous thrombosis); (iii) history of anticoagulant medications, such as warfarin, aspirin, rivaroxaban, and low molecular heparin; (iv) history or preoperative condition of abnormal liver function, acute or chronic renal failure, heart failure, NYHA > III, or ASA (American Society of Anesthesiologists) score > III; and (v) inflammatory arthritis such as rheumatoid arthritis or preoperative signs of infection (abnormal level of CRP, IL-6, white blood cells and so on)

The patient screening and enrollment process is shown in the diagram in Fig. 1.

Randomization and Treatment

Computerized block randomization was performed by an independent research assistant who was not involved in the study. Sealed envelopes were distributed to the participants at a 1:1 ratio and were opened by the assistant just prior to the start of surgery.

Patients in the EACA group received 120 mg/kg EACA in 100 ml saline intravenously prior to the anesthesia. After closing the joint capsule, 2 g topical EACA in 50 ml saline was applied through the drain tube and the drainage was kept clamped for 30 min until the end of surgery. Further, three doses of 40 mg/kg IV EACA in 100 ml saline was utilized at the 0, 3, 6 h after surgery.

Patients in the TXA group received 20 mg/kg TXA in 100 ml saline intravenously prior to the anesthesia. After closing the joint capsule, 1 g topical TXA in 50 ml saline was applied through the drain tube and the drainage was kept clamped for 30 min until the end of surgery. Further, three doses of 20 mg/kg IV TXA in 100 ml saline was utilized at the 0, 3, 6 h after surgery.

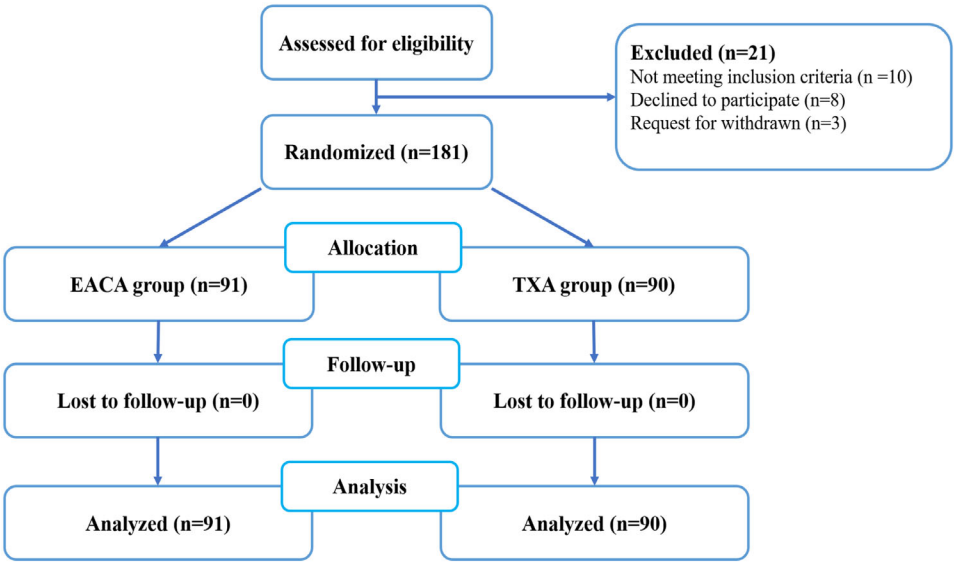

Fig. 1 Flow diagram of patients' selection and exclusion

Tourniquet was not used on any patient in the groups. A drainage tube was placed to the surgery site for each patient, which was kept unclamped postoperatively and removed 24 h after the surgery.

Surgical Procedures, Blood Management and Anticoagulation Strategy

All patients underwent routine preoperative preparations. The surgeries were performed by the same surgeon and the same surgical technique was used throughout the study. A limited median anterior knee incision was made and a para-medial approach to the patella was used in all cases. Routine femoral (intramedullary guide) and tibial (extramedullary guide) preparations were carried out and the TKAs were performed using the standard measured-resection technique. Electrocautery was used to minimize intraoperative blood loss. A cemented, posterior stabilized, fixed-bearing TKA prosthesis was used in all cases (Depuy Synthes, Warsaw, IN, USA).

Patients were given transfusions when HB < 70 g/L or had any signs of anemia. No patients received EPO, iron supplements or folic acid perioperatively. Every patient received postoperative low molecular-weight heparin (0.3 ml QD, Clexane, Sanofi-Aventis, Lyon, France) until discharge with the first half dose launched 6 h postoperatively. After the discharge, oral Rivaroxaban (10 mg QD; Xarelto, Bayer, Leverkusen, Germany) was given for 15 days. Doppler ultrasound examination was used to detect deep vein thrombosis at 5 and 30 days after surgery. Pulmonary embolism (PE) was diagnosed on the basis of chest CT scans.

Outcome Measurements and Data Collection

The primary outcomes were total blood loss (TBL), transfusion rates and drop of hemoglobin level. The secondary outcomes included postoperative hospital stays and postoperative complications. TBL was calculated according to the formula of Sehat:[25] TBL = patient's blood volume (PBV) × (Hctpre-Hctpost)/ Hctave (Hctpre = preoperative Hct level; Hctpost = postoperative Hct level; Hctave = the average of the Hctpre and Hctpost). PBV was calculated according to the formula used by Nadler:[26] PBV = (k1 × height (m) + k2 × weight (kg) + k3) × 1000, (k1 = 0.3669, k2 = 0.03219, and k3 = 0.6041 for men; and k1 = 0.3561, k2 = 0.03308, and k3 = 0.1833 for women).

Baseline clinical characteristics of enrolled patients were collected preoperatively. HB and HCT levels were recorded at 1, 3 and 5 days after surgery. Length of postoperative hospital stays and complications were recorded.

Statistical Analysis

Sample size calculations were performed using PASS 2011 software (NCSS, LLC, Kaysville, UT, USA). As a primitive study described by Xie *et al.*,[27] the total blood loss was 677.6 ± 326 ml, with a dosage of 20 mg/kg TXA before skin incision and 10 mg/kg IV TXA 3 and 6 h postoperatively. A difference of 200 ml in TBL was installed as a benchmark to justify the efficiency of EACA during primary TKA with a power of 0.90 and a significance level of 0.05, hence 47 patients per group were required.

Statistical analysis was conducted with SPSS software (Version 26.0; SPSS Inc., Chicago, IL, USA). Continuous variables were presented as the mean and standard deviation. Followed by evaluation for normality using the Kolmogorov–Smirnov test and normality plots, the baseline demographic and clinical variables were compared using independent-samples *t*-tests or Mann–Whitney tests. Categorical variables were summarized as frequencies and percentages and were measured using chi-square tests. Complication rates were compared using Fisher exact tests.

TABLE 1 Demographic and clinical characteristics

Demographics	TXA (n = 90)	EACA (n = 91)	*P* value
Age (years)	66.31 ± 6.64	66.44 ± 7.49	0.897
Gender			0.119
Female	78(85.71)	69(76.67)	
Male	13(14.29)	21(23.33)	
BMI (kg/m^2)	25.39 ± 3.68	25.07 ± 3.20	0.530
ASA			1.000
1	0(0.00)	1(1.11)	
2	70(76.92)	69(76.67)	
3	21(23.08)	20(22.22)	
HB0 (g/L)	133.02 ± 14.95	131.06 ± 13.02	0.538
HCT0 (L/L)	0.40 ± 0.04	0.40 ± 0.04	0.497
ALB0 (g/L)	44.79 ± 3.28	46.55 ± 14.08	0.246
CR0 (mg/dl)	67.14 ± 16.64	66.95 ± 14.65	0.935
INR0	0.95 ± 0.06	0.94 ± 0.06	0.739
APTT0 (S)	26.84 ± 3.20	27.13 ± 4.27	0.613
PLT0 (109/L)	180.00(142.00 - 225.50)	176.00(145.00 - 231.00)	0.895

Abbreviations: ALB0, preoperative albumin; APTT0, preoperative APTT; CR0, preoperative creatinine; INR0, preoperative INR; HB0, preoperative hemoglobin; HCT0, preoperative hematocrit; PLT0, preoperative platelet.

Results

A total of 181 patients were included for randomization and analysis, with 91 in the EACA group and 90 in the TXA group. There were no significant differences between the two groups concerning the demographic characteristics (Table 1). The mean age was 66.44 ± 7.49 years in EACA group and 66.31 ± 6.64 years in TXA group. The mean BMI was 25.07 ± 3.20 kg/m^2 in EACA group and 25.39 ± 3.68 kg/m^2 in TXA group. EACA group consisted of 21 males and 69 females, while TXA group consisted of 13 males and 78 females. The mean preoperative HB and HCT levels were 133.02 ± 14.95 g/L and 0.40 ± 0.04 in TXA group and 131.06 ± 13.02 g/L and 0.40 ± 0.04 in EACA group. For preoperative coagulation function, the mean INR and APTT were 0.95 ± 0.06 and 26.84 ± 3.20 s in TXA group and 0.94 ± 0.06 and 27.13 ± 4.27 s in EACA group.

Blood Conserving Effect

With respect to primary outcomes, the total blood loss in EACA group was higher than that in TXA group with a significant difference (1065.49 ml *vs* 831.83 ml, $P = 0.015$; Table 2). HB level decreased postoperatively in both groups to a different degree (Fig. 2). The HB level of patients in the EACA group was generally lower than that of patients in the TXA group (HB1: 105.18 ± 13.02 g/L *vs* 112.64 ± 13.11 g/L, $P = 0.002$; HB3: 95.59 ± 13.71 g/L *vs* 101.74 ± 12.07 g/L, $p = 0.009$; Table 3). Similarly, the HB drop of patients in EACA group was higher than that of patients in the TXA group (ΔHB1: 24.99 ± 9.40 g/L *vs* 20.84 ± 9.48 g/L, $P = 0.004$; ΔHB3: 35.46 ± 12.26 g/L *vs* 31.28 ± 11.19 g/L, $P = 0.047$). No patient met the criteria for transfusions. Thus, no one was given blood transfusions in the EACA and TXA groups.

Complications

In terms of the postoperative complications, although three patients suffered intramuscular venous thrombosis, superficial cellulitis and allergy in EACA group (Table 4), there was no significant difference between the two groups. However, the risk for nausea and vomiting was significantly higher in the TXA group than the EACA group (11/90 *vs* 0/91,

TABLE 2 Blood conservation effect

	TXA	EACA	*P* value
PBV0 (ml)	3826.78 ± 702.67	3754.77 ± 586.63	0.455
TBL (ml)	831.83 (661.73–1070.13)	1065.49 (704.04–1391.23)	0.015
Transfusion (%)	0 (0)	0 (0)	
Postoperative hospital stays (days)			
2	42 (46.15)	1 (1.11)	
3	44 (48.35)	43 (47.78)	
4	4 (4.40)	36 (40.00)	
5	0 (0.00)	6 (6.67)	
6	1 (1.10)	4 (4.44)	
Mean (SD)	2.62 ± 0.68	3.66 ± 0.81	<0.001

Abbreviations: PBV0, preoperative patient's blood volume; TBL, total blood loss

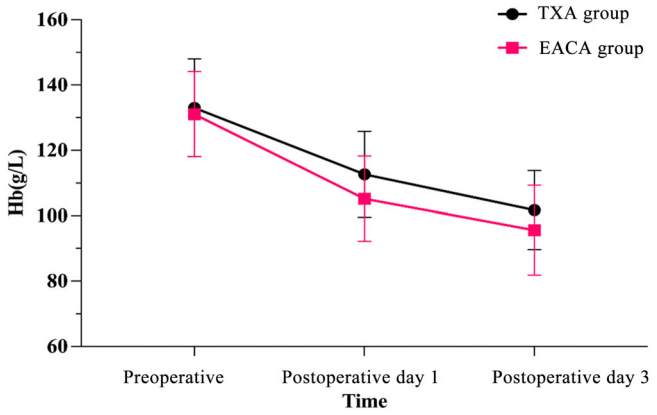

Fig. 2 Preoperative and postoperative HB levels; the error bars represent 95% CIs

TABLE 3 Hemoglobin Level

	TXA	EACA	*P*-value
HB0	133.02 ± 14.95	131.06 ± 13.02	0.428
HB1	112.64 ± 13.11	105.18 ± 13.02	0.002
HB3	101.74 ± 12.07	95.59 ± 13.71	0.009
ΔHB1	20.84 ± 9.48	24.99 ± 9.40	0.004
ΔHB3	31.28 ± 11.19	35.46 ± 12.26	0.047

Abbreviations: EACA, epsilon-aminocaproic acid; HB0, preoperative hemoglobin; HB1, hemoglobin at day 1 after surgery; HB3, hemoglobin at day 3 after surgery; TXA, tranexamic acid; HBΔHB1 = HB0-HB1; ΔHB3 = HB0-HB3

TABLE 4 Perioperative complications

	TXA	EACA	*P*-value
DVT	0 (0.00)	0 (0.00)	1.000
IMVT	0 (0.00)	1 (1.11)	0.497
PE	0 (0.00)	0 (0.00)	1.000
Superficial cellulitis	0 (0.00)	1 (1.11)	0.497
Dislocation	0 (0.00)	0 (0.00)	1.000
Allergy	0 (0.00)	1 (1.11)	0.497
Severe nausea and vomiting	11 (12.22)	0 (0.00)	<0.01
Acute renal failure	0 (0.00)	0 (0.00)	1.000
Epilepsy	0 (0.00)	0 (0.00)	1.000

Abbreviations: DVT, deep venous thrombosis; EACA, epsilon-aminocaproic acid; IMVT, Intramuscular venous thrombosis; PE, pulmonary embolism; TXA, tranexamic acid.

$P < 0.01$). No other adverse events, such as DVT, PE, stroke, acute renal failure or epilepsy occurred in this trial.

Postoperative Hospital Stays

The length of postoperative stays in EACA group was longer than that in TXA group (3.66 ± 0.81 days *vs* 2.62 ± 0.68 days, $P < 0.001$; Table 2). Most patients were discharged 3 days after surgery, with 44 patients (48.53%) in the TXA group and 43 patients (47.78%) in the EACA group. 42 (46.15%) patients in TXA group were discharged 2 days after surgery, while 36 (40.00%) patients in EACA group were discharged 4 days after surgery.

Discussion

We performed a high-quality, randomized, controlled trial to compare EACA with TXA in the multiple dose IV/IA combinational administration, and found that EACA can be an alternative to TXA in reducing blood loss in TKA, especially for patients with severe nausea and vomiting. We obtained the relative blood conserving effects of EACA versus TXA, and provided a new mode of EACA administration and potential clinical value in controlling bleeding for patients undergoing TKA.

Efficacy of EACA and TXA in the IV/IA Combined Administration

The main controversy over TXA is about its optimal dosage and administration. To achieve a better outcome in reducing bleeding and transfusion rates, some studies on TXA simply investigated the effect of dose increase and only focused on the potential risk for thrombosis. The combinational use of a higher dose of TXA and anticoagulant drugs was developed to achieve a better outcome and keep the risk of thrombosis low simultaneously. However, it is not definitive whether the statistical difference found in the blood loss and HB drop was clinically significant. In addition, the risks of complications for excessive TXA use remains unclear except for thrombosis. It was hard to define the phrase "better enough". As for EACA, its dosage, administration and effectiveness are less reported in total joint surgery. Although some studies have compared EACA with TXA in joint surgeries,[20,28] its optimal usage and its efficacy compared to TXA are still controversial.

In most circumstances, TXA is given intravenously, topically or combined. Several studies have investigated the safety and efficacy of TXA in reducing blood loss in TKA through the three abovementioned administration routes. It is concluded that both topical and intravenous TXA are effective and equally safe in reducing blood loss and transfusion rates.[29–32] But there is controversy over whether the combination of intravenous and topical application of TXA has a better outcome in reducing blood loss than topical or intravenous TXA alone. A systematic review and meta-analysis conducted by Liu *et al.*[33] including six studies involving 682 patients compared the efficacy and safety of the combined IV and topical use of TXA to the IV-TXA alone for total hip arthroplasty. Another systematic review and meta-analysis including seven RCTs with 972 patients after TKA is conducted by Wang *et al.*[34] Both of them concluded that the combined application of TXA resulted in less blood loss compared to the administration through a single route without increasing risk of postoperative complications.

TABLE 5 Previously reported results of EACA in total joint arthroplasty

	Participants		Intervention		Total blood loss (ml)	
Year	EACA	Contrast	EACA	Contrast	EACA	Contrast
2001 THA[40]	26	29	150 mg/kg IV EACA preoperatively + 12.5 mg/kg/h EACA IV for 5 h	placebo	867	1198
2006 TKR[41]	32	35	100 mg/kg IV EACA before tourniquet deflation + 1 g/h IV EACA for 3 h	10 mg/kg IV TXA before the tourniquet was deflated and 3 h later	1104	1095
2016 THA[35]	80	80	5 g topical EACA + 100 ml NS intraoperatively	placebo	1403	1603
2017 TKA[20]	96	98	7 g IV EACA before tourniquet inflation + 7 g IV EACA at wound closure	1 g IV TXA before tourniquet inflation + 1 g IV TXA at wound closure	1101	956
2017 TKA[42]	820	610	5 g IV EACA (<50 kg) or 10 g IV EACA (>50 kg) before tourniquet deflation	1 g IV TXA before tourniquet deflation	NA	NA
2017 TKA[43]	160	80	5 g topical EACA before or after tourniquet deflation	Placebo	1424	1078
2018 TJA[44]	184	185	5 g IV EACA before incision + 5 g IV EACA during closure	Placebo	NA	NA
2019 TKA[28]	72	73	5 g IV EACA before incision + 5 g IV EACA during closure	1 g IV TXA before incision + 1 g IV TXA during closure	891.2	660.6
2020 TKA[45]	45	46	100 mg/kg IV EACA before incision + 100 mg/kg IV EACA 3 h later	Placebo	990	2710
2021 THA[46]	46	46	2 g oral EACA 2 h before surgery and 6 and 12 h after surgery	1.3 g oral TXA 2 h before surgery and 6 and 12 h after surgery	853	705

	Number of given transfusions		DVT or PE			
Year	EACA	Contrast	EACA	Contrast	Conclusion	Study type
2001 THA[40]	4	7	0	0	EACA administration can reduce blood loss and transfusion rates	RCT
2006 TKR[41]	4	1	0	0	Antifibrinolytic agents produce a significant decrease in blood loss in patients undergoing TKR	RCT
2016 THA[35]	10	23	0	0	EACA is safe and effective in reducing blood loss and cost-efficient in THA	RCS
2017 TKA[20]	0	0	1 DVT + 3 PE	1 PE	EACA may be an acceptable alternative to TXA for blood conservation following TKA	RCT
2017 TKA[42]	23	24	0	0	Utilization of EACA for TKA proved to be comparable to TXA	RCS
2017 TKA[43]	5	3	0	0	Epsilon-aminocaproic acid significantly reduces blood loss after TKA when topically applied before tourniquet release	RCS
2018 TJA[44]	5	47	1 DVT	1 DVT	EACA reduce hemoglobin loss and transfusion rates after TJA without an obvious increase in VTE	RCS
2019 TKA[28]	1	0	1 DVT + 1 PE	2 DVT	EACA is associated with increased perioperative blood loss compared with TXA	RCT
2020 TKA[45]	7	28	0	2 PE	EACA decreased the blood loss and transfusion rates compared with no antifibrinolytic therapy in TKA	RCT
2021 THA[46]	1	0	0	0	TXA group presented an average of 140 ml less blood loss than EACA group, the difference is not clinically important	RCT

Abbreviations: THA, total hip arthroplasty; TKR, total knee revision; TKA, total knee arthroplasty; TJA, total joint arthroplasty.

Based on these findings, we chose the combined administration of TXA by adding 1 g topical TXA after the component was implanted in TKA, as described in the method section.

In our study, the patients receiving EACA had a more significant HB level decrease and a more significant total blood loss than those receiving TXA. Although the difference in blood loss (233.66 ml) and post-operative HB level was statistically significant, it was deemed clinically irrelevant given that no patient required transfusion. In addition, the patients in the EACA group may have been subjected to underdosing compared with patients in the TXA group. TXA is 7–10 times more potent than EACA,[35,36] while the total dosage of EACA in our study was <5 times that of TXA used in this study. Thus, a larger dose of EACA might be more beneficial concerning the postoperative blood loss reduction.

Safety of EACA and TXA in this Study

To avoid the risks associated with a single dosage of the high amount of TXA, postoperative TXA was administered in multi doses. At our center, multiple doses of intravenous TXA significantly reduced blood loss compared with a single dose of intravenous TXA.[27] In contrast to other centers, we have used a relatively small number of TXA postoperatively considering that postoperative fibrinolysis lasts as long as 18–24 h.[37,38] The administration of TXA in this study was similar to previous trials. For EACA, considering the similar half-life of the two drugs, the timing and number of dosing of EACA were the same as TXA.

Given the short half-life of EACA (<2 h) and TXA (1.9–2.7 h),[35,36] 1 month follow-up was sufficient for collecting postoperative complications. In our study, we observed no DVT or PE, and only one intramuscular venous thrombosis occurred in one patient in the EACA group. Moreover, the low rates of superficial cellulitis and allergy showed no significant difference between the two groups. However, the risk of severe nausea and vomiting was significantly higher in the TXA group (11/90 *vs* 0/91, $P < 0.01$), which was consistent with results from other studies.[13,14] The neurokinin 1 receptor–mediated pathway has been proposed as the potential mechanism behind TXA-evoked emesis.[39]

A New Mode of EACA Application

Table 5 listed previously reported results of IV and topical administration of EACA in total joint arthroplasty surgery. Most researchers selected the IV administration of EACA, by using 100–150 mg/kg or 5 g IV EACA before surgery and 3–5 g IV EACA for 3–5 h after the surgery. Two studies chose the topical route of EACA to reduce blood loss by adding 5 g EACA intraoperatively. The maximum dose of EACA was 10–14 g in the previous studies.

Combination of intravenous and intra-articular application of EACA with postoperative multi doses was hardly reported in joint surgery. In our trial, 2 g of EACA was used topically, 120 mg/kg EACA was used for IV administration before the surgery, and 40 mg/kg IV EACA was used at the timing of 0, 3, 6 h after surgery, a total dose of EACA approximately was 14 g. Based on the results of our study, the combinational application of EACA and multiple small doses of intravenous EACA postoperatively may be a new administration scheme for EACA to achieve better efficacy.

Strengths and Limitations

There are some strengths in the current study. To our knowledge, this is the first study to make comparisons of TXA and EACA in the combination of intravenous and intra-articular application in TKA. Our work proposed a new and effective mode of EACA application, and enriched the blood conserving strategies for patients undergoing TKA, especially for those with severe nausea and vomiting.

This study also has certain limitations. First, a placebo or control group was not included in our study. However, TXA has been proved effective in TKA and the aim of this study was to compare EACA and TXA in IV/IA combinational administration. Second, the efficacy of EACA in reducing blood loss may be underestimated when compared to TXA in this study. Since TXA is 7–10 times more potent than EACA, further studies are needed to optimize the dosage of EACA.

Conclusion

Although the TBL and HB drop were slightly greater in EACA group, these results were not clinically important, given that no transfusions were required. EACA could be an alternative to TXA, especially for patients with severe nausea and vomiting after using TXA postoperatively. Further studies are needed to adjust dosage of EACA to make better comparison of the two drugs.

Author Contributions

Bin Shen, Jun Ma and Che Zheng conceived and performed the experiments. Jiawen Xu and Yuan Liu contributed to data acquisition. Mingyang Li and Haibo Si analyzed and interpreted the data. Bin Shen, Jun Ma and Che Zheng revised the manuscript. All authors read and approved the final manuscript.

Acknowledgments

We thank the nursing team and operating room staff in the Department of Orthopedics of West China Hospital, Sichuan University for their assistance in this work.

Funding Information

This study was supported through grants from the Key Project of Sichuan Science & Technology Department (2020YFS0139).

Conflict of interests

The authors declare that they have no conflict of interests.

References

1. Sloan M, Premkumar A, Sheth NP. Projected volume of primary Total joint arthroplasty in the U.S., 2014 to 2030. J Bone Joint Surg Am. 2018;100(17):1455–60.
2. Sultan AA, Cantrell WA, Rose E, Surace P, Samuel LT, Chughtai M, et al. Total knee arthroplasty in the face of a previous tuberculosis infection of the knee: what do we know in 2018? Expert Rev Med Devices. 2018;15(10):717–24.
3. Worland RL, Johnson G, Alemparte J, Jessup DE, Keenan J, Norambuena N. Ten to fourteen year survival and functional analysis of the AGC total knee replacement system. Knee. 2002;9(2):133–7.
4. Sculco TP. Global blood management in orthopaedic surgery. Clin Orthop Relat Res. 1998;357:43–9.
5. Cardone D, Klein AA. Perioperative blood conservation. Eur J Anaesthesiol. 2009;26(9):722–9.
6. Kwak J, Wilkey AL, Abdalla M, Joshi R, Roman PEF, Greilich PE. Perioperative blood conservation: guidelines to practice. Adv Anesth. 2019;37:1–34.
7. Reikerås O, Clementsen T. Time course of thrombosis and fibrinolysis in total knee arthroplasty with tourniquet application. Local versus systemic activations. J Thromb Thrombolysis. 2009;28(4):425–8.
8. Sassoon A et al. Tranexamic acid: optimal blood loss management in surface replacement arthroplasty. Bone Joint J. 2016;98-b(2):173–8.
9. Gandhi R, Evans HMK, Mahomed SR, Mahomed NN. Tranexamic acid and the reduction of blood loss in total knee and hip arthroplasty: a meta-analysis. BMC Res Notes. 2013;6:184.
10. Pachauri A, Acharya KK, Tiwari AK. The effect of tranexamic acid on hemoglobin levels during total knee arthroplasty. Am J Ther. 2014;21(5):366–70.
11. Kakiuchi H, Kawarai-Shimamura A, Fujii Y, Aoki T, Yoshiike M, Arai H, et al. Efficacy and safety of tranexamic acid as an emetic in dogs. Am J Vet Res. 2014;75(12):1099–103.
12. Orito K et al. Safety and efficacy of intravenous administration for tranexamic acid-induced emesis in dogs with accidental ingestion of foreign substances. J Vet Med Sci. 2017;79(12):1978–82.
13. Preston JT, Cameron IT, Adams EJ, Smith SK. Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia. Br J Obstet Gynaecol. 1995;102(5):401–6.
14. Tengborn L, Blombäck M, Berntorp E. Tranexamic acid–an old drug still going strong and making a revival. Thromb Res. 2015;135(2):231–42.
15. Eubanks JD. Antifibrinolytics in major orthopaedic surgery. J Am Acad Orthop Surg. 2010;18(3):132–8.
16. Hardy JF, Desroches J. Natural and synthetic antifibrinolytics in cardiac surgery. Can J Anaesth. 1992;39(4):353–65.
17. Ray M et al. Aprotinin and epsilon aminocaproic acid are effective in reducing blood loss after primary total hip arthroplasty–a prospective randomized double-blind placebo-controlled study. J Thromb Haemost. 2005;3(7):1421–7.
18. Oppenheimer AJ, Ranganathan K, Levi B, Strahle JM, Kapurch J, Muraszko KM, et al. Minimizing transfusions in primary cranial vault remodeling: the role of aminocaproic acid. J Craniofac Surg. 2014;25(1):82–6.
19. Martin K, Knorr J, Breuer T, Gertler R, MacGuill M, Lange R, et al. Seizures after open heart surgery: comparison of ε-aminocaproic acid and tranexamic acid. J Cardiothorac Vasc Anesth. 2011;25(1):20–5.
20. Boese CK, Centeno L, Walters RW. Blood conservation using tranexamic acid is not superior to epsilon-aminocaproic acid after Total knee arthroplasty. J Bone Joint Surg Am. 2017;99(19):1621–8.
21. Guerreiro JPF et al. Intraarticular epsilon aminocaproic acid versus tranexamic acid IN total knee arthroplasty. Acta Ortop Bras. 2021;29(6):312–5.
22. Morales-Avalos R, Ramos-Morales T, Espinoza-Galindo AM, Garay-Mendoza D, Peña-Martínez VM, Marfil-Rivera LJ, et al. First comparative study of the effectiveness of the use of tranexamic acid against ε-aminocaproic acid via the Oral route for the reduction of postoperative bleeding in TKA: a clinical trial. J Knee Surg. 2021;34(4):383–405.
23. Huang Z, Ma J, Shen B, Pei FX. Combination of intravenous and topical application of tranexamic acid in primary total knee arthroplasty: a prospective randomized controlled trial. J Arthroplasty. 2014;29(12):2342–6.
24. Jain NP, Nisthane PP, Shah NA. Combined Administration of Systemic and Topical Tranexamic Acid for Total knee arthroplasty: can it Be a better regimen and yet safe? A randomized controlled trial. J Arthroplasty. 2016;31(2):542–7.
25. Sehat KR, Evans RL, Newman JH. Hidden blood loss following hip and knee arthroplasty. Correct management of blood loss should take hidden loss into account. J Bone Joint Surg Br. 2004;86(4):561–5.
26. Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery. 1962;51(2):224–32.
27. Xie J, Ma J, Yao H, Yue C, Pei F. Multiple boluses of intravenous tranexamic acid to reduce hidden blood loss after primary Total knee arthroplasty without tourniquet: a randomized clinical trial. J Arthroplasty. 2016;31(11):2458–64.
28. Bradley KE, Ryan SP, Penrose CT, Grant SA, Wellman SS, Attarian DE, et al. Tranexamic acid or epsilon-aminocaproic acid in total joint arthroplasty? A randomized controlled trial. Bone Joint J. 2019;101-b(9):1093–9.
29. Juraj M, Jaroslav V, Gažová A, Žufková V, Kyselovič J, Šteňo B. Evaluation of efficacy and safety of systemic and topical intra-articular administration of tranexamic acid in primary unilateral total hip arthroplasty. Medicine (Baltimore). 2021;100(26):e26565.
30. Zhang X, Ma D, Pan J, Wen L. Effects of different applications of tranexamic acid on perioperative blood transfusion rate and postoperative pain in unilateral Total knee arthroplasty. Adv Ther. 2021;38(2):1143–54.
31. Palija S, Bijeljac S, Manojlovic S, Jovicic Z, Jovanovic M, Cvijic P, et al. Effectiveness of different doses and routes of administration of tranexamic acid for total hip replacement. Int Orthop. 2021;45(4):865–70.
32. Tsukada S, Kurosaka K, Nishino M, Maeda T, Hirasawa N, Matsue Y. Intraoperative intravenous and intra-articular plus postoperative intravenous tranexamic acid in Total knee arthroplasty: a placebo-controlled randomized controlled trial. J Bone Joint Surg Am. 2020;102(8):687–92.
33. Liu X, Liu J, Sun G. A comparison of combined intravenous and topical administration of tranexamic acid with intravenous tranexamic acid alone for blood loss reduction after total hip arthroplasty: a meta-analysis. Int J Surg. 2017;41:34–43.
34. Wang Z, Shen X. The efficacy of combined intra-articular and intravenous tranexamic acid for blood loss in primary total knee arthroplasty: a meta-analysis. Medicine (Baltimore). 2017;96(42):e8123.
35. Sucher MG, Giordani M, Figoni A, Nedopil AJ. Peri-operative blood-loss after total hip arthroplasty can be significantly reduced with topical application of epsilon-aminocaproic acid. Int Orthop. 2016;40(10):2019–23.
36. Blaine KP, Press C, Lau K, Sliwa J, Rao VK, Hill C. Comparative effectiveness of epsilon-aminocaproic acid and tranexamic acid on postoperative bleeding following cardiac surgery during a national medication shortage. J Clin Anesth. 2016;35:516–23.
37. Blanié A, Bellamy L, Rhayem Y, Flaujac C, Samama CM, Fontenay M, et al. Duration of postoperative fibrinolysis after total hip or knee replacement: a laboratory follow-up study. Thromb Res. 2013;131(1):e6–e11.
38. Xie J, Ma J, Kang P, Zhou Z, Shen B, Yang J, et al. Does tranexamic acid alter the risk of thromboembolism following primary total knee arthroplasty with sequential earlier anticoagulation? A large, single center, prospective cohort study of consecutive cases. Thromb Res. 2015;136(2):234–8.
39. Kantyka ME, Meira C, Bettschart-Wolfensberger R, Hartnack S, Kutter APN. Prospective, controlled, blinded, randomized crossover trial evaluating the effect of maropitant versus ondansetron on inhibiting tranexamic acid-evoked emesis. J Vet Emerg Crit Care (San Antonio). 2020;30(4):436–41.
40. Harley BJ et al. The effect of epsilon aminocaproic acid on blood loss in patients who undergo primary total hip replacement: a pilot study. Can J Surg. 2002;45(3):185–90.
41. Camarasa MA, Ollé G, Serra-Prat M, Martín A, Sánchez M, Ricós P, et al. Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: a randomized clinical trial. Br J Anaesth. 2006;96(5):576–82.
42. Churchill JL et al. Comparing ε-aminocaproic acid and tranexamic acid in reducing postoperative transfusions in Total knee arthroplasty. J Knee Surg. 2017;30(5):460–6.
43. Harper RA, Sucher MG, Giordani M, Nedopil AJ. Topically applied epsilon-aminocaproic acid reduces blood loss and length of hospital stay after Total knee arthroplasty. Orthopedics. 2017;40(6):e1044–9.
44. Hobbs JC, Welsby IJ, Green CL, Dhakal IB, Wellman SS. Epsilon aminocaproic acid to reduce blood loss and transfusion after Total hip and Total knee arthroplasty. J Arthroplasty. 2018;33(1):55–60.
45. Tripathy SK, Rao PB, Nanda SN, Nayak C, Samal BP, Jain M, et al. Safety and efficacy of epsilon aminocaproic acid (EACA) as an antihemorrhagic drug in bilateral one stage total knee arthroplasty: a double-blind randomized controlled trial. Knee. 2020;27(1):229–34.
46. Morales-Avalos R, Ramos-Morales T, García-Pedro JA, Espinoza-Galindo AM, Acosta-Olivo C, Morcos-Sandino M, et al. Tranexamic acid versus aminocaproic acid in multiple doses via the oral route for the reduction of postoperative bleeding in total primary hip arthroplasty: a prospective, randomized, double-blind, controlled study. Blood Coagul Fibrinolysis. 2021;32(2):132–9.