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Perioperative blood loss of sequential administration of hemocoagulase Agkistrodon and Tranexamic acid for primary total knee arthroplasty: a randomized controlled trial

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Abstract

Purpose Total knee arthroplasty (TKA) has significant perioperative blood loss and a high transfusion rate. Tranexamic acid (TXA) has widely recognized hemostatic efficacy in TKA. Hemocoagulase Agkistrodon (HCA) enhances coagulation by hydrolyzing fibrinogen into fibrin, complements the hemostatic effect of TXA. Our aim was to investigate the hemostatic potential of sequential administration of HCA and TXA in TKA.

Methods Patients who underwent cemented total knee arthroplasty at our hospital were randomized to receive the sequential administration of HCA and TXA ($n=29$) or TXA-only ($n=30$. All patients received mechanical and chemical thromboprophylaxis protocol. The primary outcome was perioperative blood loss, while secondary outcomes were postoperative coagulation function and arterio-venous thrombosis, transfusion, and complications.

Results Total blood loss was not different between sequential administration of HCA and TXA group (1,025.3 ± 305.3 mL) and TXA-only group (892.4 ± 306.4 mL, $P=0.079$). Intermuscular vein thrombosis was reported in one case in the sequential administration group and three cases in the TXA-only group. No deep vein thrombosis was reported in any of the patients. The two groups had no perioperative transfusion.

Conclusion The sequential administration of HCA and TXA does not demonstrate superior efficacy in reducing blood loss compared to TXA-only. However, the HCA and TXA group has a lower incidence of intermuscular thrombosis and may demonstrate superiority in postoperative thromboprophylaxis.

Keywords Total knee arthroplasty, Hemocoagulase Agkistrodon, Blood loss, Tranexamic acid

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Background

Total knee arthroplasty (TKA) is the first choice for end-stage knee osteoarthritis patients [1, 2, 3, 4]. However, TKA has a high perioperative bleeding and a high rate of postoperative allogeneic transfusion. The average perioperative blood loss can range from 1,000 to 2,000 mL, with postoperative allogeneic blood transfusion rates varying between 10% and 40% [5–8]. The significant blood loss contributes to increased perioperative complications and imposes a prolonged hospital stay time on patients [7, 9]. To minimize perioperative blood loss and reduce the risk of transfusion, the use of pharmacological hemostasis is one of the effective ways in clinical practice [10].

Tranexamic acid (TXA), a fibrinolytic inhibitor, effectively prevents surgery-induced hyperfibrinolysis [11]. TXA has been shown to reduce perioperative blood loss and decrease the rate of transfusion in TKA, without increasing the risk of postoperative venous thromboembolism (VTE) [12, 13, 14, 15]. The hemostatic effect of TXA in TKA is widely confirmed.

Intravenous injectable hemocoagulase Agkistrodon (HCA) is a single component hemocoagulase, with a mechanism of action distinct from that of TXA [16]. By hydrolyzing fibrinogen to fibrin, HCA significantly enhances the coagulative potential of damaged blood vessels [17]. Thus, intravenous injectable HCA and TXA have complementary hemostatic effects. The efficacy and safety of HCA has been well-documented in abdominal surgery and hip hemiarthroplasty [18, 19], however, there is a gap in the research data on HCA administration in TKA.

Consequently, we established a hemostatic protocol involving the sequential administration of HCA and TXA in TKA. The combination of these two interventions is expected to provide effective perioperative bleeding control, with a reduced risk of adverse effects due to their different targets on coagulation pathways [20]. Our study aims to evaluate the efficacy and safety of the sequential administration of HCA and TXA in perioperative blood loss, intraoperative blood loss and postoperative management.

Methods

Patients and randomization

This study has been reported in line with Consolidated Standards of Reporting Trials (CONSORT 2010) Guidelines. This single-center, double-blind, randomized controlled trial was approved by the Biomedical Ethics Committee of our institution. Inclusion criteria encompassed patients undergoing TKA for knee osteoarthritis at our institution between July 17, 2022 and October 13, 2023. Each patient provided written informed consent before surgery.

Patients were excluded if they had a history of deep vein thrombosis, arterial thrombosis, cerebrovascular thrombosis or infarction, or pulmonary embolism within the past six months, had thrombosis of the popliteal proximal veins, or significant stenosis of the lower limb atherosclerosis shown by preoperative ultrasound, had a history of knee infection, had coagulopathy, refused to participate in the study.

Prior to TKA, patients were randomized to A or B groups: The HCA 1 IU was administered intravenously 15 to 20 min before surgery, and tranexamic acid 1,000 mg was administered intravenously at six hours after surgery in group A; tranexamic acid 20 mg/kg was administered intravenously 15 to 20 min before surgery; and tranexamic acid 1,000 mg was administered intravenously at six hours after surgery in group B [21]. Random numbers were generated using a computer algorithm and sealed in opaque envelopes. Each patient was asked to select one envelope, inside which their group allocation was indicated. Data collectors who gathered postoperative information were not involved in the surgical procedure and were blinded to the group allocation.

Anesthesia and surgery

Our surgical team including two senior orthopedic surgeons performed all the TKAs. All patients received general anesthesia [22]. A standard medial parapatellar approach and measured resection technique with a cemented total knee prosthesis system [23] were used for all patients undergoing TKA (DePuy Sigma PFC, Johnson and Johnson, New Brunswick, USA). The intramedullary guides were used for femoral preparation and the extramedullary guides for tibial preparation. No intraarticular drainage tube was applied in any of the patients. No tourniquets were used in any of the patients.

Postoperative management and thromboembolism prophylaxis protocol

All patients received a personalized venous thromboprophylaxis protocol recommended by the American Society of Hematology (ASH) 2019 guidelines for management of venous thromboembolism [24]. For mechanical prophylaxis, all patients received intermittent compression devices and lower extremity strength training daily during hospitalization. And all patients were instructed to postoperative walk on the day of surgery. As for chemical prophylaxis, rivaroxaban 10 mg (10 mg, Xarelto, Bayer, Germany) was administered orally once daily for 30 days after surgery if no bleeding events occurred. Coagulation and Doppler ultrasound of both lower extremities was monitored on postoperative days one to three and two weeks postoperatively. The computed tomography (CT) was used to diagnose pulmonary embolism (PE) on postoperative day three.

Blood transfusions were guided by clinical transfusion protocols [25], reserved for patients presenting with hemoglobin levels below 70 g/L, or those with levels below 100 g/L accompanied by anemic symptoms (weakness, palpitations, pallor, tachycardia, shortness of breath due to anemia). Albumin transfusions were reserved for patients whose serum albumin concentrations below 35 g/L for two consecutive days postoperatively.

Data extraction and outcomes assessment

The primary outcome included total blood loss (TBL), intraoperative blood loss (IBL), and hidden blood loss (HBL). The TBL was calculated using the Gross formula [26]:

$$\mathrm{TBL} = \mathrm{PBV} \times (\mathrm{Hct}_{\mathrm{pre}} - \mathrm{Hct}_{\mathrm{post}})/\mathrm{Hct}_{\mathrm{avg}}$$

where PBV is the predicted blood volume; $\mathrm{Hct}_{\mathrm{pre}}$ is the preoperative Hct level; and $\mathrm{Hct}_{\mathrm{post}}$ is the lowest postoperative Hct level. $\mathrm{Hct}_{\mathrm{avg}}$ is the mean of $\mathrm{Hct}_{\mathrm{pre}}$ and $\mathrm{Hct}_{\mathrm{post}}$. PBV was calculated using the following formula [27]:

$$\mathrm{PBV} = [\mathrm{k1} \times \mathrm{height}\,(\mathrm{m})^3] + [\mathrm{k2} \times \mathrm{weight}\,(\mathrm{kg})] + \mathrm{k3}$$

where k1 = 0.3669, k2 = 0.03219, and k3 = 0.6041 for men, or k1 = 0.3561, k2 = 0.03308, and k3 = 0.1833 for women. The HBL was defined as the TBL and the difference between IBL.

Statistical analysis

Referring to the study [28], the TBL with TXA-only was 803.7 ml, with standard deviations (SD) of 321.8 ml. We hypothesized that a reduction of at least 300 ml in TBL would be considered clinically significant with the combination of HCA and TXA. The test power (1-β) was set to 0.9, and the significance level (α) was 0.05. The expected loss to follow-up rate was 5%. Based on these parameters, calculations indicated that a minimum of 27 patients per group would be required to achieve statistical significance.

Continuous variables are presented as means ± SD, while categorical variables are expressed as frequencies. Inter-group differences were assessed for significance using the Mann–Whitney *U* tests for continuous data that were skewed or exhibited unequal variance, or by independent samples *t*-tests for continuous data that were normally distributed. Categorical variables were analyzed with *Chi*-square or Fisher's exact tests. A significance level of $P < 0.05$ was considered statistically significant. And 95% confidence interval (CI) of the mean difference (MD) as well as test efficacy (Cohen's D) were performed. All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS, version 26.0; IBM, Armonk, NY, USA).

Results

In our study, 68 patients were initially candidates for cemented TKA. However, nine patients declined to participate in the study. We finally enrolled 59 patients in the study, allocating 29 patients to the sequential administration of HCA and TXA groups and 30 patients to the TXA-only groups (Fig. 1). All patients were followed up for at least three months. The two groups did not different significantly in preoperative demography characteristics (Table 1). TBL (HCA and TXA, 1025.3 ± 305.3 mL; TXA-only, 892.4 ± 306.4 mL; $P = 0.079$), IBL (HCA and TXA, 148.3 ± 60.5 mL; TXA-only, 133.3 ± 56.2 mL; $P = 0.328$), HBL (HCA and TXA, 877.0 ± 294.6 mL; TXA-only, 759.0 ± 282.4 mL; $P = 0.122$) did not reach statistical significance in two groups. The hemoglobin was higher in HCA and TXA group (110.9 ± 11.0 g/L) than in TXA-only group (107.6 ± 12.5 g/L, $P = 0.032$) on the postoperative day two. And All patients had no perioperative transfusion. Only one calf muscular venous thrombosis in HCA and TXA group, but three in TXA-only group ($P > 0.05$). And All patients had no DVT, PE (Table 2).

Fibrinogen on postoperative day one in HCA and TXA group (3.2 ± 0.6 g/L) was lower than TXA-only group (3.5 ± 0.6 g/L, $P = 0.044$). And FDP on postoperative day one in HCA and TXA group (12.5 ± 6.1 mg/L) was higher than TXA-only group (6.0 ± 3.4 mg/L, $P < 0.001$). However, FDP and fibrinogen on postoperative day two and week two were not different between two group ($P > 0.05$). D-dimers on postoperative day one (7.1 ± 5.2 mg/L) and day two (2.2 ± 0.9 mg/L) in HCA and TXA group was higher than TXA-only group (2.5 ± 2.7 mg/L, $P < 0.001$; 1.7 ± 0.6 mg/L, $P = 0.040$). However, D-dimers on postoperative week two were not different between two group ($P > 0.05$) (Table 3).

Stratified analysis showed in HCA and TXA group TBL of female was higher than TXA-only group ($P = 0.035$) in HCA and TXA group, and high BMI (> 27: $P = 0.05$), high preoperative platelet count (> 200*10^9/L: $P = 0.009$), long preoperative thrombin time (> 17 s: 0.041), and low preoperative fibrinogen (< 3 g/L: 0.039) has higher TBL in HCA and TXA group (Table 4). Figure 2 showed the results of the linear regression of BMI and TBL, with a significant correlation in HCA and TXA group ($\beta = 0.374$, standard $t = 2.093$, $P = 0.046$), TBL was the dependent variable, but not in TXA-only group ($\beta = 0.107$, standard $t = 0.568$, $P = 0.575$).

Discussion

To facilitate a more accurate comparison of the safety and efficacy of the sequential administration of HCA and TXA regimen with the existing perioperative pharmacologic hemostatic regimen, we administered an appropriate dosage of TXA to the control group in accordance with the guidelines [21]. Our study revealed that

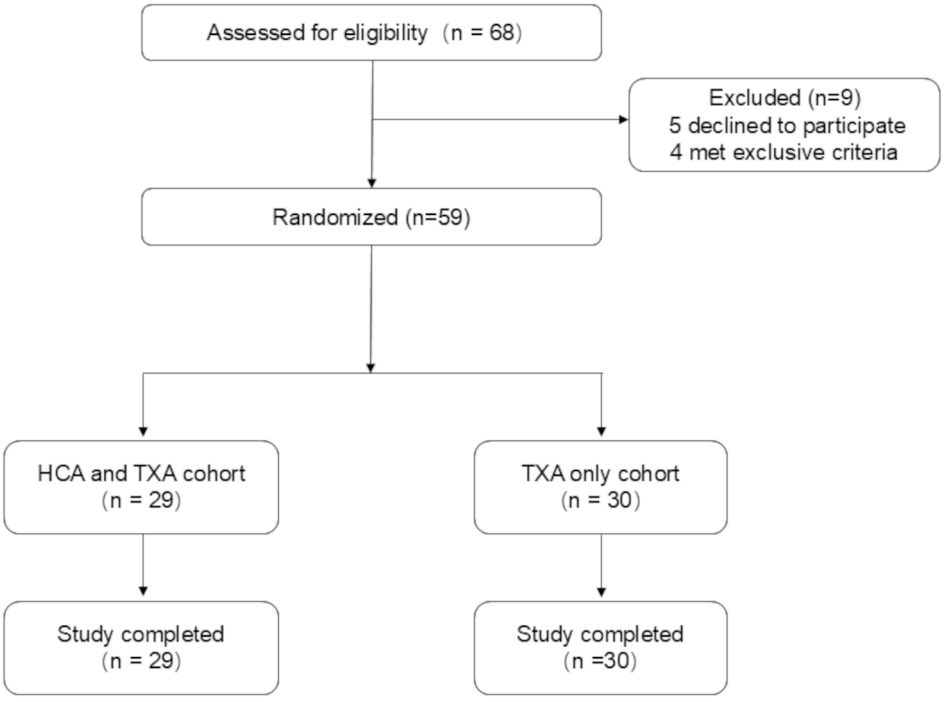

Fig. 1 Flowchart of patient enrollment

sequential administration of HCA and TXA for perioperative hemostasis in TKA showed a trend toward higher blood loss in the HCA and TXA group, although this did not reach statistical significance, and none of patients had postoperative transfusions. IBL in the two groups was 148.3 and 133.3 ml, we considered no clinical difference. Although the HBL was 120 ml higher in the HCA and TXA group than in the TXA-only group, it was also not clinically significant. The postoperative hemoglobin in the HCA and TXA group decreased by 5–7 g/L more than in the TXA-only group, which would not have been clinically different, and none of them reached the transfusion threshold. Surprisingly, our study showed that the incidence of postoperative venous thromboembolism in sequential administration of HCA and TXA group was lower than that in TXA-only group, suggeted that HCA may be of greater benefit to patients with high risk of thrombosis.

Hemocoagulase is a protein-based hemostatic agent derived from snake venom, with several studies reporting its clinical applications [20, 29, 30]. Studies have shown that hemocoagulase exerts hemostatic effects specifically at the sites of vascular injury, without interfering with the normal physiological coagulation system [31, 32]. Moreover, the fibrin clot is rapidly degraded by the fibrinolytic system, minimizing the risk of thrombosis and demonstrating satisfactory targeting. Hemocoagulase has demonstrated marked hemostatic efficacy and safety in abdominal surgery, as well as in hemiarthroplasty and spinal fusion [18, 19, 33]. Additionally, a spinal surgery study has demonstrated that this combination significantly reduces perioperative blood loss [20].

HCA is a thrombin-like enzyme derived from the venom of the *Chinese Deinagkistrodon acutus*[17]. Several researches have demonstrated that the hemostatic mechanism of HCA accelerates hemostasis at the wound site by promoting fibrinogen degradation and facilitating the intravascular production of higher concentrations of soluble fibrin [17, 34]. This process does not induce the aggregation of insoluble fibrin complexes, thereby preventing thrombosis in normal blood vessels. HCA's hemostatic mechanism is distinct from that of TXA, an analog of the amino acid lysine, which exerts its antifibrinolytic effect by competitively inhibiting plasminogen activation and plasmin binding to fibrin [35]. As evidenced by our finding that the sequential administration of HCA and TXA group exhibited fewer postoperative thrombotic events (Table 2). However, this outcome may also be attributed to the underdosing of TXA in the group.

Our results indicated that on the postoperative day one, levels of FDP and D-dimers were significantly higher in the sequential administration of HCA and TXA group compared to the TXA-only group, while FIB was significantly lower. This is consistent with previous studies [17, 36], which suggest that HCA degrades FIB and produces fibrin for coagulation without preventing fibrin degradation, thus FIB and D-dimers are elevated. (Table 3). From

Table 1 Baseline demography characteristics in two cohorts

Projects	HCA and TXA ($n=29$)	TXA only ($n=30$)	*P* value
Age (years) [a]	65.9 ± 7.8	66.3 ± 6.2	0.812
Gender (male/female) [b]	23-Jun	24-Jun	> 0.999
BMI [a]	26.4 ± 2.5	27.0 ± 3.1	0.4
Length of hospitalization (days) [a]	6.0 ± 0.5	6.1 ± 0.4	0.536
Postoperative hospital stay (days) [a]	3.1 ± 0.3	3.1 ± 0.4	0.839
Comorbidities [b]			
Hypertension	9	8	0.779
Diabetes	2	2	> 0.999
Chronic bronchitis	1	0	> 0.999
Anemia	0	1	> 0.999
Autoimmune disease	1	1	> 0.999
Osteoporosis	11	13	0.793
Preoperative laboratory values [a]			
Hematocrit (%)	41.7 ± 2.8	41.6 ± 3.6	0.98
Hemoglobin (g/L)	133.5 ± 11.2	133.9 ± 13.5	0.898
Platelet counts (10^9/L)	204.1 ± 63.2	188.5 ± 54.4	0.313
Thrombin time (s)	17.2 ± 0.8	17.1 ± 0.7	0.772
APTT (sec)	25.7 ± 2.3	25.6 ± 2.0	0.835
INR	0.97 ± 0.05	0.95 ± 0.06	0.284
PT (sec)	10.7 ± 0.6	10.5 ± 0.7	0.485
Fibrinogen(g/L)	2.9 ± 0.6	3.0 ± 0.4	0.699
FDP(mg/L)	2.8 ± 1.3	2.9 ± 1.9	0.742
D-dimers (mg/L)	0.71 ± 1.12	0.57 ± 0.49	0.889
Total protein (g/L)	72.4 ± 4.1	72.2 ± 4.6	0.622
Albumin(g/L)	45.7 ± 3.2	45.6 ± 2.9	0.876
CRP (mg/L)	4.2 ± 2.1	3.6 ± 2.6	0.133
IL-6 (pg/ml)	4.2 ± 2.8	3.3 ± 1.6	0.163
Pain VAS score [a]	5.2 ± 1.8	4.9 ± 1.1	0.305

[a] The values are given as mean ± standard deviation; [b] The values are given as numbers;

BMI, body mass index; APTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time; FDP, fibrin degradation products; CRP, C-reactive protein; IL-6, interleukin 6; VAS, visual analogue scale;

the postoperative day two onward, FDP and D-dimers levels gradually returned to similar levels in both two groups (Table 3). Additionally, there were no significant differences in preoperative and postoperative coagulation values, such as TT, APTT, and PT (Table 3). Therefore, we suggest that the sequential administration of HCA and TXA does not adversely affect the patients' coagulation function.

Additionally, hemocoagulase may induce hypofibrinogenemia, which requires immediate correction in patients with fibrinogen levels below 1.5 g/L, which may lead to varying degrees of hepatic impairment [37]. Ma et al. reported an incidence of hypofibrinogenemia of 0.97% in HCA [38]. In our sequential administration of HCA and TXA group, the mean postoperative fibrinogen level was consistently above 3 g/L (Table 3), with no patients experiencing levels below 1.5 g/L. The mean postoperative albumin level in this group was also greater than 35 g/L (Table 2), indicating that the liver's ability to synthesize both fibrinogen and albumin remained intact. Therefore, we can infer that the HCA and TXA regimen exhibits lower hepatotoxicity.

TXA has excellent hemostatic effects during the perioperative period of TKA [39], effectively reducing perioperative blood loss, transfusion rates, and postoperative acute inflammatory reactions [40, 41, 42]. However, HCA promotes fibrinogenolysis and produces FDP, FDP promotes postoperative inflammatory response [43, 44, 45, 46]. Surprisingly, our findings revealed no significant differences in CRP and IL-6 levels between the two groups on postoperative days one and two, probably because the combination of HCA and TXA did not lead to an excessive inflammatory response. Therefore, we suggest that our sequential administration of HCA and TXA does not exacerbate the acute postoperative inflammatory response, and patients do not experience significant postoperative pain, and can reduce the risk of postoperative infections [47, 48, 49].

Our results also indicated no significant difference in postoperative complications between the two groups. The sequential administration of HCA and TXA did not increase the incidence of postoperative wound bleeding or adverse wound events, and no postoperative blood transfusions were required in either group. Based on these findings, we can suggest that the sequential administration of HCA and TXA do not increase the risk of bleeding in TKA, while also reducing the risk of postoperative thrombosis compared to the administration of TXA only. Qin et al. also reported that the use of hemocoagulase possessed a lower incidence of venous thrombosis than TXA [50].

Our stratified analysis showed gender, BMI, preoperative platelet count, preoperative thrombin time, and preoperative fibrinogen were all confounders affecting TBL in the HCA + TXA group. A majority of patients undergoing TKA are elderly females, with a enhanced thrombin generation and significantly diminished fibrinolytic activity compared to their male counterparts [51]. Thus, smaller doses of TXA and injections of exogenous thrombin did not reach similar effects as in older men. Additionally, HBL was calculated in relation to body weight and height. In the TXA only group, the dose administered was adjusted preoperatively according to the patient's weight, whereas in the HCA and TXA group, the dose administered was fixed at 1 IU irrespective of body weight. This may result in underdosing of the group in high BMI samples [52, 53]. And, our linear regression analysis of BMI and TBL in both groups showed a significant linear relationship between TBL and BMI in the HCA and TXA group. However, no such relationship in the TXA-only group. Patients with lower perioperative fibrinogen and poorer perioperative prothrombin time

Table 2 Perioperative blood loss, postoperative laboratory test, transfusion and complications in two cohorts

Projects	HCA and TXA ($n=29$)	TXA only ($n=30$)	MD (95%CI)	*P* value	Cohen'D
Duration of surgery (min) [a]	77.2 ± 12.5	76.6 ± 11.2	0.6(-5.6-16.7)	0.907	0.04
IBL (mL) [a]	148.3 ± 60.5	133.3 ± 56.2	15.0(-15.4-45.3)	0.328	0.26
TBL (mL) [a]	1025.3 ± 305.3	892.4 ± 306.4	132.9(-26.6-294.4)	0.079	0.44
HBL (mL) [a]	877.0 ± 294.6	759.0 ± 282.4	118.0(-32.4-268.4)	0.122	0.41
Hemoglobin (g/L) [a]					
Postoperative 4 h	117.7 ± 10.7	123.4 ± 13.8	-5.7(-12.2-0.7)	0.081	-0.47
Postoperative day 1	106.7 ± 11.0	111.3 ± 12.6	-4.6(-10.8-1.5)	0.134	-0.4
Postoperative day 2	100.9 ± 11.0	107.6 ± 12.5	-7.6[-12.9-(-0.6)]	0.032	-0.57
Postoperative day 14	125.0 ± 10.8	126.3 ± 12.8	-1.3(-8.0-5.4)	0.7	-0.11
Albumin (g/L) [a]					
Postoperative day 1	39.0 ± 1.9	39.1 ± 1.8	-0.1(-1.1-0.8)	0.772	-0.08
Postoperative day 2	37.3 ± 2.0	37.7 ± 1.8	-0.4(-1.3-0.6)	0.46	-0.19
Postoperative day 14	45.6 ± 1.9	45.7 ± 1.7	-0.1[-0.4-(-0.1)]	0.805	-0.07
Transfusion (U) [a]	0	0	NA	NA	NA
Postoperative CRP (mg/L) [a]					
Postoperative day 1	48.8 ± 33.5	45.1 ± 33.8	3.7(-13.8-21.3)	0.655	0.11
Postoperative day 2	104.9 ± 52.0	94.2 ± 60.4	10.7(-18.7-40.2)	0.282	0.19
Postoperative day 14	3.8 ± 1.9	3.4 ± 2.6	0.4(-0.7-1.7)	0.083	0.21
Postoperative IL-6 (pg/ml) [a]					
Postoperative day 1	99.8 ± 105.4	99.6 ± 87.3	0.2(-50.2-50.6)	0.555	0.01
Postoperative day 2	65.6 ± 36.3	57.9 ± 34.0	7.7(-10.6-26.1)	0.405	0.22
Postoperative day 14	3.9 ± 3.0	3.2 ± 1.9	0.7(-0.6-2.0)	0.307	0.29
Pain VAS score [a]					
Postoperative day 1	4.7 ± 1.4	4.5 ± 1.3	0.2(-0.5-0.8)	0.741	0.12
Postoperative day 2	4.0 ± 0.9	4.0 ± 1.0	-0.0(-0.5-0.5)	0.881	-0.04
Postoperative day 14	1.2 ± 1.2	1.2 ± 1.1	0.0(-0.2-0.7)	0.996	0.45
Complications [b]					
DVT	0	0	NA	NA	/
CMVT	1	3	0.5(0.1–1.5) [c]	0.612	/
PE	0	0	NA	NA	/
incision infection	0	0	NA	NA	/
Incision bleeding	2	1	1.3(0.4–2.3) [c]	0.612	/
Peri-incision bruise	1	1	1.0(0.2–2.1) [c]	> 0.999	/
Allergic reaction	0	0	NA	NA	/
Abnormal function of liver	0	0	NA	NA	/
Abnormal function of kidney	0	0	NA	NA	/

[a] The values are given as mean ± standard deviation; [b] The values are given as numbers;[c] The values are given as RR (95%CI); MD: mean difference; CI: confidence interval; RR: relative risk

TBL, total blood loss; IBL, intraoperative blood loss; HBL, hidden blood loss; DVT, deep vein thrombosis; PE, pulmonary embolism; CRP, C-reactive protein; IL-6, interleukin 6; VAS, visual analogue scale; CMVT, Calf muscular venous thrombosis

would have a poorer response to exogenous prothrombin, resulting in higher blood loss.

Finally, the postoperative sequential administration intervals of TXA exceeded the therapeutic window relative to HCA's pharmacokinetics, particularly given HCA's shorter half-life [54]. This mismatch in timing resulted in a failure to demonstrate a synergistic hemostatic effect when sequential administrated TXA and HCA. Future studies should prioritize larger cohorts, incorporate rigorous control of confounding variables, and optimize HCA dosing protocols, including adjusted intervals and dosage. Intravenous HCA delivery offers advantages over intra-articular injection, enabling more precise dose titration, reduced risk of joint cavity accumulation, and minimized hypersensitivity risks.

Conclusion

Overall, our study introduces a novel perioperative hemostatic regimen for TKA. Although the sequential administration of HCA and TXA had a slightly less control blood loss effect than the preoperative and postoperative TXA only, there was no increase in the rate of transfusion or risk of postoperative bleeding. Furthermore, the sequential administration of HCA and TXA experienced a lower incidence of venous thrombosis. For patients at elevated risk of thrombosis, this perioperative

Table 3 Postoperative platelet counts and coagulation laboratory values in two cohorts

Projects	HCA and TXA (*n* = 29)	TXA only (*n* = 30)	MD(95%CI)	*P* value	Cohen's D
Postoperative platelet counts (10^9/L)					
Postoperative day 1	178.1 ± 50.0	170.1 ± 55.5	8.0(-20.0-36.2)	0.566	0.17
Postoperative day 2	171.2 ± 45.1	167.8 ± 48.5	3.4(-21.0-27.8)	0.781	0.11
Postoperative day 14	267.1 ± 78.7	253.8 ± 78.5	13.3(-28.1-54.6)	0.523	0.17
Postoperative thrombin time (sec)					
Postoperative day 1	16.0 ± 1.0	16.1 ± 0.7	-0.1(-0.6-0.3)	0.925	0.87
Postoperative day 2	15.2 ± 0.5	15.3 ± 0.6	-0.1(-0.4-0.2)	0.681	0.55
Postoperative day 14	16.9 ± 0.9	16.8 ± 0.6	0.1(-0.3-0.4)	0.494	0.76
Postoperative APTT (sec)					
Postoperative day 1	26.3 ± 2.2	26.3 ± 2.3	-0.0(-1.2-1.2)	0.982	-0.01
Postoperative day 2	27.7 ± 3.2	28.7 ± 2.8	-1.0(-2.6-0.5)	0.186	-0.35
Postoperative day 14	25.3 ± 1.8	26.2 ± 2.1	-0.9(-1.9-0.2)	0.098	-0.44
Postoperative INR					
Postoperative day 1	1.03 ± 0.09	1.03 ± 0.09	0.00(-0.04-0.02)	0.772	0.02
Postoperative day 2	1.04 ± 0.10	10.6 ± 0.08	-0.02(-0.06-0.02)	0.542	-0.16
Postoperative day 14	1.02 ± 0.06	1.03 ± 0.05	-0.01(-0.04-0.02)	0.636	-0.12
Postoperative PT (sec)					
Postoperative day 1	11.5 ± 1.0	11.5 ± 1.1	-0.0(-90.6-0.5)	0.687	-0.31
Postoperative day 2	11.5 ± 1.0	11.6 ± 0.9	-0.1(-0.6-0.4)	0.623	-0.24
Postoperative day 14	10.9 ± 0.7	11.1 ± 0.6	-0.2(-0.5-0.2)	0.319	-0.64
Postoperative fibrinogen(g/L)					
Postoperative day 1	3.2 ± 0.6	3.5 ± 0.6	-0.3(-0.6-0.0)	0.044	-0.61
Postoperative day 2	4.8 ± 1.0	5.3 ± 1.2	-0.5(-1.1-0.0)	0.066	-0.49
Postoperative day 14	3.2 ± 0.6	3.5 ± 0.5	-0.3(-0.6-0.0)	0.074	-0.48
Postoperative FDP(mg/L)					
Postoperative day 1	12.5 ± 6.1	6.0 ± 3.4	6.5(4.0-9.1)	< 0.001	1.33
Postoperative day 2	6.0 ± 2.2	5.2 ± 1.8	0.8(-0.3-1.8)	0.269	0.37
Postoperative day 14	9.1 ± 6.1	9.4 ± 5.8	-0.3(-3.4-2.8)	0.732	-0.05
Postoperative D-dimers (mg/L)					
Postoperative day 1	7.1 ± 5.2	2.5 ± 2.7	4.6(2.5–6.9)	< 0.001	1.1
Postoperative day 2	2.2 ± 0.9	1.7 ± 0.6	0.5(0.1–0.8)	0.04	0.55
Postoperative day 14	5.5 ± 2.6	5.6 ± 2.8	-0.1(-1.4-1.2)	0.904	-0.03

The values are given as mean ± standard deviation; MD: mean difference; CI: confidence interval

APTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time; FDP, fibrin degradation products;

hemostatic management strategy may offer a more effective approach to reducing the risk of perioperative thrombosis.

Table 4 Stratified analysis of factors for TBL in different subgroups

Stratification factors	MD ± SD of TBL (*n*)		*P* value	Cohen's D
	HCA and TXA (*n*=29)	TXA only (*n*=30)		
Gender				
Male	1130.7 ± 390.0 (*n*=6)	1134.5 ± 437.5 (*n*=6)	0.988	-0.09
female	997.8 ± 283.3 (*n*=23)	831.8 ± 240.1 (*n*=24)	0.035	0.63
age (years)				
≤65	1037.0 ± 264.5 (*n*=13	926.8 ± 159.5 (*n*=12)	0.225	0.5
>65	1015.8 ± 343.3 (*n*=16)	869.4 ± 377.2 (*n*=18)	0.248	0.41
BMI (Kg/m^2)				
≤25	881.3 ± 224.3 (*n*=8)	882.7 ± 257.4 (*n*=8)	0.99	-0.01
25-27	942.6 ± 287.4 (*n*=11)	861.1 ± 199.2 (*n*=9)	0.481	0.33
>27	1231.4 ± 291.7 (*n*=10)	920.0 ± 400.2 (*n*=13)	0.05	0.87
Hemoglobin baseline (g/L)				
≤135	998.2 ± 260.7 (*n*=16)	778.1 ± 247.7 (*n*=17)	0.018	0.87
>135	1058.7 ± 361.1 (*n*=13)	1041.8 ± 320.0 (*n*=13)	0.901	0.05
Platelet counts baseline (10^9/L)				
≤200	949.1 ± 368.4 (*n*=14)	933.0 ± 348.4 (*n*=16)	0.903	0.05
>200	1096.4 ± 221.9 (*n*=15)	845.9 ± 255.0 (*n*=14)	0.009	1.05
Thrombin time baseline (sec)				
≤17	1013.3 ± 234.8 (*n*=12)	996.0 ± 360.3 (*n*=13)	0.889	0.06
>17	1033.7 ± 353.6 (*n*=17)	813.2 ± 239.6 (*n*=17)	0.041	0.73
APTT baseline (sec)				
≤25	855.8 ± 274.2 9 (*n*=10)	849.8 ± 194.2 (*n*=8)	0.961	0.02
>25	1114.7 ± 288.1 (*n*=19)	938.1 ± 368.8 (*n*=16)	0.121	0.54
PT baseline (sec)				
≤10.5	986.6 ± 272.7 (*n*=12)	836.7 ± 238.5 (*n*=18)	0.122	0.59
>10.5	1052.6 ± 331.8 (*n*=17)	975.9 ± 383.3 (*n*=12)	0.57	0.22
Fibrinogen baseline(g/L)				
≤3	1037.8 ± 344.0 (*n*=17)	813.2 ± 281.4 (*n*=19)	0.039	0.72
>3	1007.6 ± 254.1 (*n*=12)	1029.0 ± 312.0 (*n*=11)	0.858	-0.01

The values are given as mean ± standard deviation;

BMI, body mass index; APTT, activated partial thromboplastin time; PT, prothrombin time

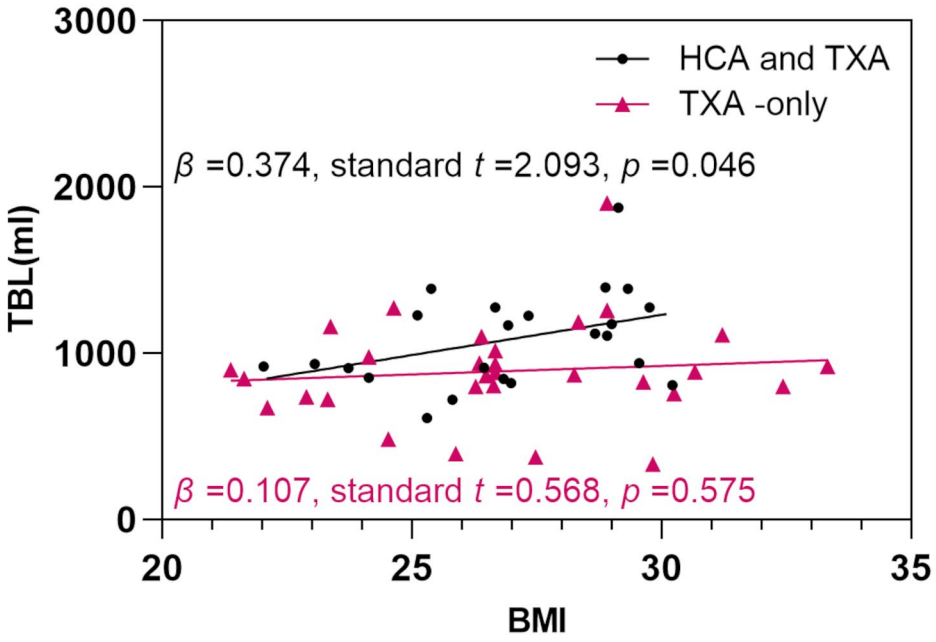

Fig. 2 Regression analysis of BMI and TBL for both two cohorts, with TBL as the dependent variable. $P < 0.05$ in the HCA and TXA cohort. The statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS, version 26.0; IBM, Armonk, NY, USA)

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Author contributions
The first two authors are co-first authors, the two authors contributed to this article equally. All authors take responsibility for the integrity of the work as a whole. All authors have full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Conception and design: YJ, QH and FP.YJ and HL wrote the main manuscript text and WJ prepared Figs. 1 and 2. Drafting and critical revision of the article: YJ, HL and ZZ.All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The Sichuan University West China Hospital's institutional review board approved the study. Our study has registered in the Chinese Clinical Trial Registry - (ChiCTR2200058554).

Consent to participate
Informed consent was obtained from all individual participants included in the study.

Consent to publish
Our manuscript does not involve any individual person's data in any form (including any individual details, images or videos).

Competing interests
The authors declare no competing interests.

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