Combined administration of tranexamic acid and vitamin K proved perioperative blood loss reduction with cementless total hip replacement: a prospective randomized controlled study

Ahmed R. Khamis[a], Saad A. Shoulah[a], Dina H. Abdelhamid[b]

Departments of, [a]Orthopaedics and Trauma Surgery,, [b]Anaesthesia, Benha University Hospital, Benha, Egypt

Correspondence to Ahmed R. Khamis, MD, Department of Orthopaedics and Trauma Surgery, Benha University Hospital, El-Shaheed Farid Nada Street, Benha, Al Qalyubia, Postal Vode: 13511, Egypt. Tel: +20 100 238 1187; e-mail: ahmedkhames73@yahoo.com

Received: 08 August 2021
Revised: 01 February 2022
Accepted: 06 February 2022
Published: 23 September 2022

The Egyptian Orthopaedic Journal 2022, 57:138–144

Introduction
Blood loss during total joint replacement has serious implications on patients affecting their ability to immediately start the postoperative enhanced recovery program. Tranexamic acid (TA) is well known for its ability to reduce blood loss during arthroplasty. Vitamin K has an important physiological role in the clotting cascade, but its action is delayed and dose sensitive.
Study settings and design
A prospective comparative study conducted in Benha University Hospital.
Patients and methods
In all, 150 patients were randomly divided into three groups, each included 50 patients. Group A received both TA and vitamin K1, group B received only vitamin K1, and group C received only TA. Perioperative blood parameters tested included hemoglobin level, hematocrit percentage, platelet count, prothrombin time, partial thromboplastin time, and fibrinogen level. Intraoperative and postoperative blood losses and the amount of blood transfusion were reported. A surgeon satisfaction score was created to assess the degree of intraoperative bleeding.
Results
The mean perioperative differences in blood parameters and amount of blood loss were evaluated with the post-hoc test. Group A showed a statistically significant less changes in blood parameters and less blood loss than the other groups, and group B showed less postoperative blood losses.
Conclusion
Combined administration of TA and vitamin K with cementless total hip replacement proved efficient in reducing intraoperative and postoperative blood losses and the need for blood transfusion. This was reflected on the patient's ability to start the enhanced recovery program immediately, reduced the duration of postoperative hospital stay, and the overall cost of operation.

Keywords:
antifibrinolytics, bleeding, total hip, tranexamic acid, vitamin K

Egypt Orthop J 2022, 57:138–144

1110-1148

Introduction

Bleeding is a major complication that lengthens the duration of surgery and affects the postoperative recovery after orthopedic operations. Orthopedic surgeries account for up to 10% of the need for blood transfusions. Avoiding allogenic blood products protects the patient from the possible complications of blood transfusion including infection. Approximately 75–90% of the intraoperative and the early postoperative blood loss is due to surgical technical factors. Uncontrolled bleeding will lead to anemia, hemodilution, hypothermia, consumption of clotting factors, and metabolic acidosis. These effects worsen the clotting process and suppress the immune system. Blood loss in the absence of blood conservation strategies during total joint replacement increases the need for blood transfusion in about 75% of cases [1–5]. Various agents were used to reduce blood loss such as bone wax, gelatin sponges, collagen plugs, fibrin glues, and lysine analogs such as epsilon-aminocaproic acid (tranexamic acid; TA) and aprotinin [6–8]. TA is a synthetic antifibrinolytic agent that blocks binding of plasminogen to fibrin, thus delaying fibrinolysis. Its half-life is 80 min and 95% is excreted unchanged by the kidneys. It reduces blood loss during arthroplasty and scoliosis surgery, thus significantly reducing blood transfusion [9–12].

Vitamin K1 regulates hepatic synthesis and function of clotting factors II, VII, IX, and X, has effects on osteocalcin and bone matrix GLa protein, and inhibits vascular calcification. It antagonizes the effect

of warfarin with onset of action after few hours, but the liver needs 3–5 days to resynthesize the vitamin K-dependent clotting factors. This delayed onset of action makes vitamin K use limited to prevent rebleeding after hemorrhage control and for the correction of the international normalized ratio in warfarinized patients [13,14]. Many studies proved the efficacy and safety of TA in reducing blood loss with total joint replacement; however, only few studies have focused on vitamin K in the prevention of bleeding after certain surgeries.

This study investigated the impact of the combined administration of TA with vitamin K1 to reduce blood loss and the need for blood transfusion in patients undergoing primary cementless total hip replacement.

Patients and methods

This prospective, comparative randomized study was conducted in Benha University Hospital on 150 patients through the period between 2012 and 2019. Study conducted after ethical approval from the department ethical Committee and patients consent. The patients were American Society of Anesthesiologists class I and II, aged 58–73 years and their body weight ranged between 62 and 93 kg, scheduled for primary cementless total hip replacement for osteoarthritis. The patients were randomly divided into three groups each included 50 patients: group A received initial doses of intravenous TA 10 mg/kg and 10 mg vitamin K1 (10 ml intravenous infusion over 10 min) 5 min before skin incision followed by an infusion of TA 1 mg/kg/h and vitamin K1 0.2 mg/kg/h, until skin closure. Group B received intravenous 10 mg vitamin K1 (10 ml slow infusion for 10 min) 5 min before skin incision followed by infusion of 0.2 mg/kg/h until skin closure. Group C received intravenous TA 10 mg/kg 5 min before skin incision followed by an infusion of TA 1 mg/kg/h till skin closure.

Exclusion criteria included patients with American Society of Anesthesiologists class above II (severe systemic disease), a history of venous thromboembolism (VTE), allergy to any of the used drugs, abnormal preoperative coagulation profile (platelet count below 150.000/μl), prothrombin time (PT) above 16 s, partial thromboplastin time (PTT) above 60 s, patients taking drugs with known effects on coagulation, and those with contraindication to spinal anesthesia.

Venous blood samples were obtained preoperatively, intraoperatively, and 3 days postoperatively to determine hemoglobin (Hb) level, hematocrit (HTC) percentage, platelet count, PT, PTT, and fibrinogen concentration. Intraoperative, postoperative, and total blood losses together with the amount of blood transfused were recorded. Total blood loss was calculated by weighing the used surgical sponges, measuring the volume of blood suctioned from the surgical wound, estimation of blood soaking the surgical gowns and drapes, and the volume of postoperative blood loss in the suction drains. A surgeon satisfaction score was created for the degree of bleeding in the surgical field from soft tissues, femoral canal broaching, and acetabular socket reaming on a visual analog scale from 1 to 10 points, where 10 is negligible and 1 is severe bleeding. All patients received low-molecular weight heparin for 7–10 days postoperatively for prophylaxis against VTE.

Statistical analysis of the collected data of the different parameters of the study was done by the post-hoc analysis test to determine the mean differences between individual groups.

Results

Demographic data showed no statistically significant difference between groups regarding the mean age, sex, and body weight. The mean age was 65.5 years and the mean body weight was 77.5 kg. There was 83 (55.3%) males and 67 (44.6%) females (Table 1).

There was a statistically significant difference between groups regarding the mean operative time. A mean difference of 26–33 min less operative time was found in favor of groups A and C than group B. The surgeon satisfaction score was higher in groups A and C (score 7–9) than in group B (scores 4–6).

The perioperative mean Hb level in groups A and C showed less postoperative decrease in comparison with group B. This was statistically significant (P<0.001). The mean postoperative HTC percentage showed a highly statistically significant difference between groups A and C (P<0.001) in comparison to group B. The postoperative mean platelet count showed a smaller decrease in groups A and C than in group B on the third postoperative day and this was statistically significant (P<0.05). There was no statistically significant difference between groups regarding changes in PT postoperatively (P>0.05). However, groups A and B showed more reduction in the mean postoperative PT. Regarding the perioperative PTT there was no statistically significant difference between groups (P>0.05). There was no statistically significant difference between groups regarding the preoperative fibrinogen concentration (P>0.05), but there was a statistically significant difference regarding postoperative measures (P<0.05).

Table 1 Results mean values

Group/mean values	A	B	C	*P* value
Sex: female	22 (44)	30 (60)	15 (30)	>0.05
Male	28 (56)	20 (40)	35 (70)	>0.05
Age (years)	60 ± 11.3	61 ± 10.5	63 ± 10.9	>0.05
Weight (kg)	72 ± 9.5	65 ± 8.5	68 ± 6.4	
Operative time (min)	89 ± 15	127 ± 18	101 ± 23	<0.05
Surgeon satisfaction score	7–9	4–6	7–9	
Preoperative Hb (g/dl)	13.02 ± 0.497	12.90 ± 0.433	13.20 ± 0.576	<0.001
Postoperative Hb	12.54 ± 0.344	11.32 ± 0.357	12.12 ± 0.482	<0.001
Preoperative HTC %	47.90 ± 2.684	42.80 ± 1.980	47.69 ± 2.823	<0.001
Postoperative HTC	44.07 ± 2.186	37.02 ± 1.582	43.92 ± 1.772	<0.001
Preoperative platelets (10^6/ml)	360 ± 46.16	348 ± 41.91	352 ± 37.143	<0.05
Postoperative platelets	358 ± 45.26	346 ± 41.43	289 ± 127	<0.05
Preoperative PT (s)	15.59 ± 0.63	14.05 ± 0.60	13.98 ± 56	>0.05
Postoperative PT	13.34 ± 0.51	11.75 ± 0.32	13.02 ± 0.42	>0.05
Preoperative PTT (s)	33.14 ± 3.14	33.92 ± 2.92	34.02 ± 2.71	>0.05
Postoperative PTT	30.18 ± 2.75	30.89 ± 2.72	33.12 ± 1.71	>0.05
Preoperative fibrinogen (mg/dl)	358.8 ± 46.3	355.1 ± 39.5	357.11 ± 43.54	>0.05
Postoperative fibrinogen	291.2 ± 24.1	252.8 ± 23.9	300.01 ± 44.50	<0.001
Blood loss intraoperative (ml)	307.6 ± 57.6	852.3 ± 48.1	382 ± 73.06	<0.001
Postoperative drain (ml)	222.5 ± 24.6	112.5 ± 26.2	315 ± 45.52	<0.001
Total blood loss (ml)	530	964.6	697	<0.001
Cases needed transfusion	0	11	0	<0.001
Length of hospital stay (days)	3	8	5	<0.001

Data are presented as mean±SD and *n* (%). Hb, hemoglobin; HTC, hematocrit; PT, prothrombin time; PTT, partial thromboplastin time.

A statistically significant difference between groups (P<0.001) was found regarding the mean blood loss (intraoperative, postoperative, and total blood loss). Group A showed the least total blood loss, followed by group C and then group B. There was about 234 ml difference in total blood loss between groups A and B, and about 430 ml more was lost intraoperatively in group C. The mean postoperative blood loss in group B was less than the other groups (110 ml less than group A and 202.5 ml less than group C). No postoperative blood transfusion was required in groups A and B. Eleven (24%) cases in group B required one unit of intraoperative blood transfusion.

The mean duration of hospital stay was 3 days in group A, 5 days in group C, and 8 days in group B. These differences were statistically significant. No patient experienced a complication from either TA or vitamin K1, or postoperative VTE event.

Discussion

Blood loss during total joint replacement decreases the Hb level and oxygen-carrying capacity of blood, which will decrease the healing reaction, efficacy of the immune system, resistance to infection, and patient's ability to start early rehabilitation program. TA proved efficient in reducing blood loss in orthopedic surgeries through inhibiting clot breakdown without enhancing clot formation through rapid action but with a short half-life, thus not interfering with the antithrombotic prophylactic measures [2,15–18].

Intravenous vitamin K1 action is detectable within 1–2 h; hemorrhage is controlled within 3–8 h; and prothrombin level normalizes after 12–14 h. Intravenous vitamin K is preferred over the oral route due to its faster onset of action and a maximum effect within 6–12 h, compared with 12–24 h for oral preparations. Anaphylaxis with intravenous vitamin K is rare (3 : 10 000 doses) and may be due to added preservatives and fast infusion. Hypotension, arrhythmias, chest pain, collapse, decreased conscious level, or even cardiorespiratory arrest after vitamin K1 overdose were reported. Accordingly, the lowest required dose should be slowly infused to minimize the risk of anaphylaxis, though this does not completely eliminate the risk. Body stores of vitamin K1 are limited and depend on dietary intake. The main roles of vitamin K administration in surgical patients are to antagonize warfarin and prevent rebleeding after hemorrhage is controlled [19–26].

A Cochrane systematic review of TA and aprotinin use during scoliosis surgery reported reduced both autologous and allogenic blood transfusion, but evidence is insufficient to support the use of a particular agent; although TA is preferred due to its availability. The optimal doses of these agents had not been established and adverse effects may occur infrequently

with insufficient evidence to confirm the safety of these drugs [27].

Many studies have proved the safety and effectiveness of TA in reducing blood loss after total hip (primary or revision of cemented or cementless) or knee replacement and considered it as a standard of care [28–42]. Several randomized controlled studies found that intravenous, topical, and oral TA in single or multiple doses are all effective and TA is more effective than fibrin spray or sealant in reducing bleeding during hip replacement [43–53].

In our study, we used TA and vitamin K1 as an initial preoperative dose followed by continuous infusion throughout the operation. The intraoperative blood loss was reduced by about 35% and the postoperative blood loss in the suction drains by about 5% of the total amount of blood loss in groups A and C in comparison to group B. This was found to be consistent with the results of Claeys *etal*. [16], Singh *etal*. [36], Yamasaki *etal*. [38], and Yi *etal*. [54], who reported that a TA 15 mg/kg single-bolus dose reduced postoperative blood loss, total blood loss, and packed cell transfusion with total hip replacement.

The mean intraoperative blood loss in our study was 307 ml in group A, 852 ml in group B, and 382 ml in group C. This was less than the results of Malhotra *etal*. [35], who used 15 mg/kg TA single intravenous dose 15 min before skin incision in 50 primary cementless total hip arthroplasties and reported a mean of 410 ml intraoperative blood loss in comparison to 615 ml in the control group without any increased risk of thromboembolism. On the contrary, Narendra and Jeremy [41] used TA 10 mg/kg single dose at the time of anesthesia for cemented total hip arthroplasty and found no significant difference with the control group regarding blood loss from the femoral canal, perioperative bleeding, and postoperative Hb. Even in the TA group, more of their patients required blood transfusion. The difference between this study and our study is mostly due to administration of a single, low, and early dose of TA keeping in mind that the half-life of TA is 80 min.

The mean perioperative Hb level and HTC percentage changes in our study showed statistically significant decreases in groups A and C more than in group B. This was found to be consistent with the results of Singh *etal*. [36], who had a significant increase in the mean intraoperative blood loss and decrease in Hb level in the control group. They concluded that a single dose of intravenous TA 10 mg/kg 10 min before skin incision in total hip arthroplasty minimized blood loss, reduction in Hb level, and the need for allogenic blood transfusion without increasing the risk of thromboembolic events.

The mean reduction in Hb level in our study was 0.4 g/dl in group A, 1.6 g/dl in group B, and 0.6 g/dl in group C. This was reflected on the need for blood transfusion where no cases in group A or C required intraoperative transfusion, while 11 cases in group B required one unit of intraoperative transfusion. These results were better than those of Camerasa *etal*. [15] on TA efficacy during total knee replacement. They reported a mean reduction in Hb at the fifth postoperative day of 2.5 g/dl in the study group and 3.4 g/dl in the control group. This difference in favor of our study could be attributed to the fact that the bone cuts and the bleeding surfaces are much less in total hip replacement than in total knee replacement and the postoperative effects of vitamin K.

The postoperative platelet count in our study showed a statistically significant decrease in group B due to increased intraoperative blood loss and consumption of platelets in the unopposed normal clotting. These results were consistent with those of Nobuyuki *etal*. [55], who concluded that TA could protect the platelet count and function during cardiopulmonary bypass effectively without evident signs of fibrinolysis, and it reduced chest tube drainage and blood transfusion. Stephan *etal*. [5] studied the influence of bleeding on hemostasis in 122 elective orthopedic surgeries. A blood loss of more than 500 ml was associated with an increase in platelet aggregation by day 1 and day 7 after surgery and a significant decrease in platelet count concurrent with the HTC by postoperative day 1.

The mean postoperative PT and PTT in our study showed a statistically insignificant decrease among the three groups. This was consistent with the results of Azkiyah *etal*. [56] on patients with intracranial hemorrhage involving two groups; one received only TA and the other received both TA and vitamin K. They reported that patients in the second group showed a slightly more decrease in PT and PTT due to the effects of vitamin K.

The mean fibrinogen concentration in our study was lower in group B than in groups A and C. This was consistent with the studies by Zufferey *etal*. [8,9], who found less fibrin degradation products in the TA group and a statistically significant decrease in fibrinogen level in the control group.

Controversy exists regarding the optimal dose and route of administration of TA during total joint replacement. Oral, topical, intravenous, or combined

routes were used and all were effective in reducing total blood loss with the topical route being less costly [44,47,49,50]. Sershon and colleagues compared single and multiple TA doses through different routes in revision total hip arthroplasty and reported no difference in response between the different regimens. They recommended that surgeons should use the regimen that suits their practice and hospital settings. Wang and colleagues recommended one preoperative dose and three postoperative doses of TA for total hip replacement. Wilde an colleagues reported that one dose of intravenous TA was as effective as two doses in reducing blood loss and transfusion after hip or knee replacement without an increase in complication rates [51–53].

In the current study, we used TA and vitamin K intravenously as an initial dose followed by an infusion dose till wound closure to obtain the benefit of controlling blood loss during the operation through the rapid action of TA, and in the postoperative period through the delayed action of vitamin K1.

We had no reported complications from TA or vitamin K usage in our study. Hallstorm *etal*. [42] reported no evidence of increased risk of complications from TA and it was associated with a decreased rate of readmission after total hip arthroplasty, VTE after total knee arthroplasty, and no adverse effects on cardiovascular functions. A population-based cohort study did not support a relation between TA and the risk of postoperative cardiovascular complications or death after total hip replacement [57].

Several studies have proved that TA did not interfere with the use of anticoagulants and was effective and safe for reduction of bleeding and prevention of postoperative anemia in hip and knee arthroplasty patients [58–61]. However, Plaster *etal*. [62] reported a case of intraoperative anaphylactic reaction to TA during posterior spinal fusion. None of our patients had VTE complications or anaphylaxis from either drug. The body stores of vitamin K are limited and most of the elderly population are deficient in this vitamin that affects both clotting pathways and lengthens the PT and PTT values. A high oral dose and intravenous vitamin K have the same effects in reducing the risk of life-threatening intracranial bleeding in patients with vitamin K deficiency and therefore factors other than the dose should be addressed to improve efficacy [20–26,56]. Due to the delayed action of vitamin K, we found no effect of it on reduction of intraoperative blood loss in group B, but the main effects were noticed on reduction of postoperative blood loss in the suction drain. Eliwa *etal*. [63] compared the use of combined TA and vitamin K1 during scoliosis surgery to hypotensive anesthesia. They reported less blood loss with the combined TA and vitamin K1 group than in the hypotensive anesthesia group. This study did not give clear identification of the sole role of vitamin K in controlling intraoperative bleeding. Azkiyah *etal*. [56] compared the effect of coadministration of TA and vitamin K1 with the administration of TA alone on reduction of PT and PTT in patients treated for intracranial hemorrhage. They found that TA alone reduced the PTT but not the PT, while coadministration of TA and vitamin K1 significantly reduced both PT and PTT, which means more effect on both intrinsic and extrinsic clotting cascades.

Using vitamin K1 in elderly patients with possible deficiency of the vitamin could have an implication on decreasing bleeding when undergoing total joint replacement. In the current study, groups A and B showed less postoperative blood loss than group C (who took only TA) due to the delayed effect of vitamin K, while groups A and C (who took TA) showed less intraoperative and total blood losses due to the fast action of TA and the delayed action of vitamin K. This advantage allowed patients to start the rehabilitation program immediately after surgery and to be discharged from the hospital earlier than the other groups.

Conclusion

The combined administration of TA and vitamin K1 in patients undergoing cementless total hip replacement has the potential to reduce intraoperative and postoperative blood losses through the fast action of TA and the delayed action of vitamin K1. This has direct effects on the postoperative condition of patients, their ability to start the enhanced recovery program as soon as possible, duration of hospital stay, and the total cost of surgery. More studies with higher level of evidence are required to highlight any other benefits of these drugs to improve practice of the commonly performed total joint replacement.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Bechstein WO, Strey C. Local and systemic hemostasis in surgery. Chirurg 2007; 78: 95–96.

2 Eubanks DJ. Antifibrinolytics in major orthopedic surgery. J Am Acad Orthop Surg (AAOS) 2010; 18:132–138.

3 Marieta M, Facchini L, Pedrazzi P, Busani S, Torelli G. Pathophysiology of bleeding in surgery. Transplant Proc 2006; 38:812–814.

4 Müller S, Oberle. D, Bäuerle. DU, Pavel J, Stanislawski KB, Funk BM. Mortality, morbidity and related outcomes following perioperative blood transfusion in patients with major orthopedic surgery: a systematic review. Transfus Med Hemother 2018; 45:355–367.

5 Stephan B, Scenk JF, Pindur G, Meiss C, Borchers H, Nemeh A, *et al*. Influence of bleeding on haemorheology and haemostasis in surgery. J Clin Haemorheol Microcirc 2010; 46:183–188.

6 Zhao Z, Ma J, Ma X. Comparative efficacy and safety of different hemostatic methods in total hip arthroplasty: a network meta-analysis. BMC J Orthop Surg Res 2019; 14:3.

7 Ozier Y, Schlumberger S. Pharmacological approaches to reduce blood loss in surgical patients. Can J Anaesth 2006; 53(6 Suppl):S51–S59.

8 Zufferey YO, Merquiol F, Laporte S, Decousus H, Mismettip P. Do antifibrinolytic reduce allogenic blood transfusion in orthopedic surgery? Anaesthesiology 2006; 105:1034–1046.

9 Zufferey PJ, Miquet M, Quenet S, Martin P, Adam P, Albaladejo P, *et al*. Tranexamic acid in hip- fracture surgery (THIF) study. A randomized controlled trial. Br J Anaesth 2010; 104:23–30.

10 Gausden BE, Garner RM, Warner JS, Levack A, Nellestein MA, Tedore T, *et al*. Tranexamic acid in hip fracture patients: a protocol for a randomized, placebo-controlled trial on the efficacy of tranexamic acid in reducing blood loss in hip fracture patients. BMJ Open 2016; 6:e010676.

11 Yang GZ, Chen PW, Wu DL. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. J Bone Joint Surg 2012; 94:1153.

12 Tzortzopoulou A, Cepeda MS, Schumann R, Carr DB. Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children. Cochrane Database Syst Rev 2008; 3:CD006883.

13 Howland DR, Mycek JM, Harvey AR. Pharmacology (Lippincott Illustrated Reviews Series) 7th Edition; 2019, Chapter 20: 237–8. Publisher: Williams and Wilkins.

14 Wen L, Chen J, Duan L, Li S. Vitamin K?dependent proteins involved in bone and cardiovascular health (review). Mol Med Rep 2018; 18:1.

15 Camerasa MA, Olle G, Serra-Prat M, Martin A, Sanchez M, Ricos P, *et al*. Efficacy of aminocaproic, tranexamic acid in the control of bleeding in the total knee replacement: a randomized clinical study. Br J Anesth 2006; 96:576–582.

16 Claeys MA, Vermeersch N, Haentjens P. Reduction of blood loss with tranexamic acid in primary total hip replacement surgery. Acta Chir Belg 2007; 107:397–401.

17 Melvin SJ, Stryker SL, Sierra JR. Tranexamic acid in hip and knee arthroplasty. J AAOS 2015; 23:732–740.

18 Clave A, Gerard R, Lacroix J, Baynat C, des Deserts DM, Gatineau F, *et al*. A randomized, double-blind, placebo- controlled trial on the efficacy of tranexamic acid combined with Rivaroxaban thromboprophylaxis in reducing blood loss after primary cementless total hip arthroplasty. Bone Joint J 2019; 101-B:207–212.

19 Levi HJ, Tanaka AK, Dietrich W. Perioperative hemostatic management of patients treated with vitamin-K antagonists. review article. Anesthesiology 2008; 109:918–926.

20 Nascimento B, Al Mahoos M, Callum J, Capone A, Pacher J, Tien H, *et al*. Vitamin K-dependent coagulation factor deficiency in trauma: a comparative analysis between international normalized ratio and thrombo-elastography. Transfusion 2012; 52:7–13.

21 Vermeer C. Vitamin K: the effect on health beyond coagulation. Food Nutr Res 2012; 56:5329.

22 Vermeer C, Schurgers JLA. A comprehensive review of vitamin K and vitamin K antagonists. Hematol Oncol Clin North Am 2000; 14: 339–353.

23 Riegert-Johnson DL, Volcheck GW. The incidence of anaphylaxis following intravenous phytonadione (vitamin K1): a 5-year retrospective review. Ann Allergy Asthma Immunol 2002; 89:400–406.

24 Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6-Suppl):160S–198S.

25 Lubetsky A, Yonath H, Olchovsky D, Loebstein R, Halkin H, Ezra D. Comparison of oral vs intravenous phytonadione (vitamin-K1) in patients with excessive anticoagulation: a prospective randomized controlled study. Arch Intern Med 2003; 163:2469–2473.

26 Löwensteyn NY, Jansen GJN, van Heerde M, Klein HR, Kneyber JCM, Kuiper WJ, *et al*. Increasing dose of oral vitamin-K prophylaxis and its effects on bleeding. Eur J Pediatr 2019; 178:1033–1042.

27 McNicol DE, Tzortozopoulou A, Schumann R, Carr BD, Karla A. Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children. Cochrane Database Syst Rev 2016; 9:C D006883.

28 Klement RM, Padua GF, Li TW, Detweiler M, Parvizi J. Tranexamic acid reduces the rate of periprosthetic joint infection after aseptic revision arthroplasty. J Bone Joint Surg Am 2020; 102:1344–1350.

29 Kazemi SM, Mostafa F, Eajazi A, Kaffashi M, Besheli DL, Bigdeli RM, *et al*. The effect of tranexamic acid in reducing blood loss in cementless total hip arthroplasty under epidural anaesthesia. Orthopedics 2010; 33:17.

30 Ayers CD. Tranexamic acid: Both efficacious and safe when used in total hip arthroplasty to reduce blood transfusions. Commentary & perspective. J Bone Joint Surg Am 2018; 100:e135.

31 Friedman JR. Making tranexamic acid the standard of care in hip and knee arthroplasty. Commentary & perspective. J Bone Joint Surg Am 2016; 98:e86.

32 Gianakos LA, Hurley TE, Haring SR, Yoon SR, Liporace AF. Reduction of blood loss by tranexamic acid following total hip and knee arthroplasty. A meta-analysis. JBJS Rev Evid Based Syst Rev 2018; 6:e1.

33 Cai J, Ribkoff J, Olson S, Raghunathan V, Al-Samkari H, DeLoughery GT, *et al*. The many roles of tranexamic acid: an overview of the clinical indications for TXA in medical and surgical patients. Review article. Eur J Haematol 2020; 104:79–87.

34 Johansson T, Pettersson LG, Lisander B. Tranexamic acid in total hip arthroplasty saves blood and money: a randomized, double-blind study in 100 patients. Acta Orthop 2005; 76:314–319.

35 Malhotra R, Kumar V, Garg B. The use of tranexamic acid to reduce blood loss in primary cementless total hip arthroplasty. Eur J Orthop Surg Traumatol 2010; 21:101–104.

36 Singh J, Ballal MS, Mitchell P, Denn PG. Effects of tranexamic acid on blood loss during total hip arthroplasty. Jr Orthop Surg (Hong Kong) 2010; 18:282–286.

37 Sridharan K, Sivaramakrishnan G. Tranexamic acid in total hip arthroplasty: mixed treatment comparisons of randomized controlled trials and cohort studies. J Orthop 2018; 15:81–88.

38 Yamasaki S, Masuhara K, Fuji T. Tranexamic acid reduces postoperative blood loss in cementless total hip arthroplasty. J Bone Joint Surg Am 2005; 87:766.

39 Peck J, Kepecs MD, Mei B, Safir AO, Backstein D, Gross EA, *et al*. The effect of preoperative administration of tranexamic acid during revision hip arthroplasty. A retrospective study. J Bone Joint Surg 2018; 100:1509.

40 Orpen NM, Little C, Walker G, Crawfurd EJP. Tranexamic acid reduces early blood loss after total knee arthroplasty: A prospective randomized controlled trial of 29 patients. Knee 2006; 13:106–110.

41 Narendra G, Jeremy F. Bone bleeding during total hip arthroplasty after administration of tranexamic acid. J Arthroplasty 2004; 19:488–492.

42 Hallstorm B, Singal B, Cowen EM, Robert CK, Hughes ER. The Michigan experience with safety and effectiveness of tranexamic acid use in hip and knee arthroplasty. J Bone Joint Surg 2016; 98:1646.

43 Babis CG. Controversy in tranexamic acid administration route continues. Commentary & perspective. J Bone Joint Surg Am 2016; 98:e51.

44 Alshryda S, Mason J, Sarda P, Nargol A, Cooke N, Ahmad H, *et al*. Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total hip replacement. A randomized controlled trial (TRANX-H). J Bone Joint Surg 2013; 95:1969.

45 McConnell SJ, Shewale S, Munro AN, Shah K, Deakin HA, Kinninmonth WGA. Reduction of blood loss in primary hip arthroplasty with tranexamic acid or fibrin spray. A randomized controlled trial. Acta Orthop 2011; 82:660–663.

46 Mahmood A, Sawalha S, Borbora A, Kumar G, Peter V. Tranexamic acid versus fibrin sealant in primary total hip replacement: a comparative study. Eur J Orthop Traumatol 2017; 27:923–928.

47 Abdel PM, Chalmers PB, Taunton JM, Pagnano WM, Trousdale TR, Sierra J, *et al*. Intravenous versus topical tranexamic acid in total knee arthroplasty. both effective in a randomized clinical trial of 640 patients. J Bone Joint Surg 2018; 100:1023.

48 Kang XB, Xu H, Gao XC, Zhong S, Zhang J, Xie J, *et al*. Multiple dose tranexamic acid for perioperative blood loss in total knee arthroplasty in patients with rheumatoid arthritis: a single-blinded, randomized, parallel-controlled study protocol in China. BMJ Open 2020; 10:e034431.

49 Kayupov E, Fillingham AY, Okroj K, Plummer RD, Moric M, Gerlinger LT, *et al*. Oral and intravenous tranexamic acid are equivalent at reducing blood loss after total hip arthroplasty. A randomized controlled trial. J Bone Joint Surg 2017; 99:373.

50 Wong J, El Beheiry H. Topical tranexamic acid to reduce postoperative blood loss in total knee arthroplasty. JBJS Essent Surg Techniq 2011; 1:e4.

51 Sershon AR, Fillingham AY, Abdel PM, Malkani LA, Schwarzkopf R, Padgette D, *et al*. The optimal dosing regimen for tranexamic acid in revision total hip arthroplasty. a muti-center randomized clinical trial. J Bone Joint Surg 2020; 102:1883.

52 Wang D, Wang YH, Luo YZ, Pei XF, Zhou K z, Zeng NW. Finding the optimal regimen for oral tranexamic acid administration in primary total hip arthroplasty. A randomized controlled trial. J Bone Joint Surg 2019; 101:438.

53 Wilde MJ, Copp NS, McCauley CJ, Bugbee DW. One dose of intravenous tranexamic acid is equivalent to two doses in Total Hip and Knee arthroplasty. J Bone Joint Surg 2018; 100:1104.

54 Yi Z, Bin S, Jing Y, Zongke Z, Pengde K, Fuxing P. Tranexamic acid administration in primary total hip arthroplasty. A randomized controlled trial of intravenous combined with topical versus single-dose intravenous administration. J Bone Joint Surg 2016; 98:983.

55 Nobuyuki K, Yamada T, Takada J. Tranexamic acid protects platelet function and reduces bleeding in pediatric cardiac surgery. From proceedings of the 2010 annual meeting of the American Society of Anesthesiologists. 2010 Oct 19; A 1472.

56 Azkiyah ZS, Supardi S, Andrajati R. The risks of using tranexamic acid and vitamin-K for reducing prothrombin time and activated partial thromboplastin time values in intracranial hemorrhage patients. Asian J Pharm Clin Res 2017; 10:139–141.

57 Dastrup A, Pottegrad A, Hallas J, Overgaard S. Perioperative tranexamic acid and risk of cardiovascular events or death after total hip arthroplasty. A population-based cohort study from the National Danish Database. J Bone Joint Surg 2018; 100:1742.

58 Hourlier H, Fennema P. Tranexamic acid use and risk of thrombosis in regular users of anti-thrombotics undergoing primary total knee arthroplasty: a prospective cohort study. Blood Transfus 2018; 16:44–52.

59 Khan N, Troelsen A, Husted H. Prevention of postoperative anemia in hip and knee arthroplasty – a systematic review. Danish Med J 2015; 62:A5170.

60 Coobs RB, Moskal TJ. Tranexamic acid: indirect benefits to the standard of care. Commentary and perspective. J Bone Joint Surg Am. 2020; 102:e92.

61 Hunt. BJ. The current place of tranexamic acid in the management of bleeding. Review article. Anaesthesia 2015; 70(Suppl. 1):50–53.

62 Plaster S, Holy F, Antony KA. Anaphylactic reaction to tranexamic acid during posterior spinal fusion. A case-report. JBJS Case Connector 2020;10: e20.00130.

63 Eliwa H, Ismael A, Eliwa G. Blood transfusion sparing effect of co-administration of tranexamic acid and vitamin-K in scoliosis surgery. A comparison with induced hypotension. Egypt J Anesth 2004; 20:417–423.