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CLINICAL RESEARCH

Efficacy of different doses and timing of tranexamic acid in major orthopedic surgeries: a randomized trial

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KEYWORDS
Blood loss;
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Abstract
Background: Tranexamic acid was studied in four different dosage regimens and their efficacy was compared for perioperative blood loss reduction, blood transfusion requirements and deep vein thrombosis (DVT) complication.
Methods: Two hundred patients undergoing major orthopedic procedures were divided into five groups containing 40 patients each: Placebo, low dose (bolus 10 mg kg^{-1}), low dose + maintenance (bolus 10 mg kg^{-1} + maintenance 1 mg kg^{-1} hr^{-1}), high dose (bolus 30 mg kg^{-1}) and high dose + maintenance (bolus 30 mg kg^{-1} + maintenance 3 mg kg^{-1} hr^{-1}). Surgical blood loss was measured intraoperatively and drains collection in the first 24 hours postoperatively. Blood transfusion was done when hematocrit falls less than 25%. DVT screening was done in the postoperative period.
Results: The intraoperative blood loss was 440 ± 207.54 mL in the placebo group, 412.5 ± 208.21 mL in the low dose group, 290 ± 149.6 ml in the low dose plus maintenance group, 332.5 ± 162.33 mL in the high dose group and 240.7 ± 88.15 mL in the high dose maintenance group ($p < 0.001$). The reduction in postoperative blood loss in the drain for first 24 hours was 80 ± 44.44 mL in the placebo group, 89.88 ± 44.87 mL in the low dose group, 56.7 ± 29.12 mL in the low dose plus maintenance group, 77.9 ± 35.74 mL in the high dose group and 46.7 ± 19.9 mL in the high dose maintenance group ($p < 0.001$). DVT was not encountered in any patient.
Conclusion: Tranexamic acid was most effective in reducing surgical blood loss and blood transfusion requirements in a low dose + maintenance group.

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PALAVRAS-CHAVE
Perda sanguínea;
Transfusão de sangue;
Dosagem;
Posologia;
Ácido tranexâmico

Eficácia de diferentes doses e esquemas de administração de ácido tranexâmico em cirurgias ortopédicas de grande porte: estudo randomizado

Resumo
Justificativa: O ácido tranexâmico foi avaliado em quatro esquemas com diferentes posologias, comparando-se a eficácia de cada esquema quanto a redução na perda sanguínea perioperatória, necessidade de transfusão sanguínea e ocorrência de Trombose Venosa Profunda (TVP).
Método: Duzentos pacientes submetidos a procedimentos ortopédicos de grande porte foram divididos em cinco grupos de 40 pacientes de acordo com o esquema de administração de ácido tranexâmico: grupo placebo, grupo baixa dose (bolus de 10 mg kg^{-1}), grupo baixa dose e manutenção (bolus de 10 mg kg^{-1} + manutenção de 1 mg kg^{-1} h^{-1}), grupo alta dose (bolus de 30 mg kg^{-1}), e grupo alta dose e manutenção (bolus de 30 mg kg^{-1} + manutenção de 3 mg kg^{-1} h^{-1}). A perda sanguínea cirúrgica foi medida no intraoperatório. Além disso, nas primeiras 24 horas pós-operatórias foi medido o volume de sangue coletado no dreno. A transfusão de sangue era realizada se o valor do hematócrito fosse inferior a 25%. Foi realizada avaliação quanto à ocorrência de TVP no pós-operatório.
Resultados: A perda sanguínea intraoperatória foi de 440 ± 207,54 mL no grupo placebo, 412,5 ± 208,21 mL no grupo baixa dose, 290 ± 149,6 mL no grupo baixa dose e manutenção, 332,5 ± 162,33 mL no grupo alta dose, e 240,7 ± 88,15 mL no grupo alta dose e manutenção ($p < 0,001$). A redução na perda sanguínea pós-operatória pelo dreno nas primeiras 24 horas foi de 80 ± 44,44 mL no grupo placebo; 89,88 ± 44,87 mL no grupo baixa dose, 56,7 ± 29,12 mL no grupo baixa dose e dose de manutenção, 77,9 ± 35,74 mL no grupo alta dose, e 46,7 ± 19,9 mL no grupo alta dose e manutenção ($p < 0,001$). TVP não foi observada em nenhum paciente.
Conclusão: O ácido tranexâmico administrado em baixa dose combinado à manutenção foi mais eficaz em reduzir a perda sanguínea cirúrgica e a necessidade de transfusão de sangue

Introduction

The major orthopedic surgeries like spine instrumentation, Total Hip Replacement (THR) and internal fixation of femur fracture are associated with severe blood loss and may require a blood transfusion. The costs and risks associated with blood transfusion, along with difficulty in getting blood products have kindled interest in blood conservation strategies.[1] The effectiveness of tranexamic acid in reducing blood loss during major orthopedic surgeries has been proven.[2] Tranexamic Acid (TA) is a lysine analogue which inhibits the activation of plasmin thereby inhibiting tissue fibrinolysis and consequent clot stabilization. Tranexamic acid has showed a one-third reduction in blood loss in major orthopedic procedures and reduces the incidence of blood transfusion.[3]

The dosing of tranexamic acid varies from 10 to 135 mg kg^{-1}, and the duration varies from a single bolus to multiple infusions lasting up to three days.[4] Tranexamic acid has been successfully used in cardiac, liver, gynecology and orthopedic surgeries.[5] Though the efficacy of tranexamic acid in reducing blood loss has been proven in many studies, there is still no consensus on the dosing and timing of tranexamic acid administration. The anti-fibrinolytic agents like aprotinin have been associated with an increased incidence of thrombotic complications like cerebral thrombosis, myocardial infarction, and renal dysfunction.

The primary objective of this study was to compare four different dosing regimens of tranexamic acid in the reduction of blood loss intraoperatively and in the first 24 hours of the postoperative period. The secondary objectives were to compare blood transfusion requirements and the incidence of Deep Vein Thrombosis (DVT).

Patients and methods

This prospective, double-blinded, randomized, placebo-controlled clinical trial was done in a tertiary care medical college hospital after obtaining institutional ethics committee approval and written informed consent from all patients. This study was registered in Clinical Trials Registry – India (CTRI n° 2018/01/011156). Two hundred consecutive patients who underwent major hip and femur surgeries of both sexes and age groups between 18 and 70 of American Society of Anesthesiologists (ASA) physical status I and II were included in the study. The patients undergoing revision surgeries, allergic to tranexamic acid or heparin, patients with altered coagulation profile, anemia with Hemoglobin (Hb) < 10gm.%, renal and liver dysfunction, pregnant and breastfeeding women, previous deep vein thrombosis or any thrombotic complications were excluded from the study.

Patients undergoing spine instrumentation, THR, and femur fracture fixation surgery were selected. All surgeries were being operated by an experienced same surgeon for each type of surgery. The randomization was performed using a computer-generated random numbers method. The drug preparations for bolus and maintenance doses were done by the first anesthesiologist outside the operating room in apparently identical 50 mL syringes. The dose of tranexamic acid was loaded according to the group involved and made to 50 mL with Normal Saline (NS) separately for both

bolus and maintenance infusion. In the Placebo Group, only 50 mL of NS was loaded and blinding was maintained by this process of preparing identical-looking 50 mL of bolus and maintenance infusions. The second anesthesiologist, who was blinded to the group involved, administered the solution prepared separately for bolus and maintenance infusion and monitored the patient. General anesthesia was standardized for all the patients and they received patient-controlled analgesia with morphine for postoperative analgesia. The patients were randomized into five groups based on the dosage of tranexamic acid as follows:

Group L (Low dose) – Tranexamic acid 10 mg kg^{-1} bolus dose before skin incision + NS infusion until the end of the surgery.
Group LM (Low dose plus Maintenance) – Tranexamic acid 10 mg kg^{-1} bolus dose + 1 mg kg^{-1} h^{-1} infusion until the end of the surgery.
Group H (High dose) – Tranexamic acid 30 mg kg^{-1} bolus dose before skin incision + NS infusion until the end of the surgery.
Group HM (High dose + Maintenance) – Tranexamic acid 30 mg kg^{-1} bolus dose before skin incision followed by 3 mg kg^{-1} h^{-1} infusion until the end of the surgery.
Group P (Placebo) – NS before skin incision + NS infusion until the end of the surgery.

Intraoperative blood loss was calculated by weighing the surgical pads and gauzes and by measuring collection in drains. Hematocrit was monitored intraoperatively at hourly intervals and the trigger for blood transfusion was initiated when the hematocrit dropped below 25%. Postoperatively, the amount of blood loss in the drain during the first 24 hours was recorded. The amount of blood loss was compared among the groups. The need for blood transfusion and number of RBC packs used intraoperatively and in the first 24 hours after surgery were recorded and compared among the groups.

Patients were started on low molecular weight heparin 24 hours postoperatively for DVT prophylaxis. Patients were followed daily until discharge for clinical features of DVT. Doppler screening was planned in cases with clinical suspicion of DVT. The patients had extended follow-up every week for 6 weeks over the telephone to identify thrombotic complications like deep vein thrombosis, pulmonary embolism, coronary ischemia or stroke.

The sample size estimation was based on the previous study by Maniar et al.[5] For the mean difference of 250 mL of intraoperative blood loss between the groups to be identified with a standard deviation of 50 mL, a power of 80%, and alpha error at 0.05%, a minimum of 36 patients in each group were needed. Hence, we decided to include 40 patients in each group to compensate for the dropouts during the study. Data were entered in the MS-Excel spread sheet (2010) and analysed using the statistical package for social sciences version 20. Descriptive statistics including proportions, measures of dispersion and measures of central tendency were used to describe the data. The demographic profile and hemoglobin values were analysed using One-way Analysis of variance (ANOVA) test. The categorical data like sex was analysed by Chi-Square test. The intergroup comparison between the groups for intraoperative and postoperative blood loss and mean transfusion requirements were analysed by One way ANOVA test. If a significant difference among the groups was found, pairwise differences between groups were examined by the Scheffe test. A p-value of 0.05 was considered statistically significant and < 0.001 as highly significant.

Results

Two hundred and twenty-two patients were recruited into the study and a Consolidated Standards of Reporting Trials (CONSORT) flow diagram depicting the passage of participants through the study has been provided in Figure 1. There were no variations in demographic characteristics like age, sex, weight, and duration of surgery. There was no difference in preoperative hemoglobin concentration and hemoglobin concentration on the fourth postoperative day between the groups. The results were summarized in Table 1. There was no statistical significance in the type of surgeries and results were tabulated in Table 2. All the data obtained showed a normal distribution, and no skewed distribution was reported.

The intraoperative blood loss was 440 ± 207.54 mL in the placebo group, 412.5 ± 208.21 mL in the low-dose group, 290 ± 149.6 mL in the low-dose plus maintenance group, 332.5 ± 162.33 mL in the high-dose group and 240.7 ± 88.15 mL in the high-dose maintenance group. The p-value was < 0.001 and it was statistically highly significant. The intraoperative blood loss was significantly less in low dose maintenance group ($p \leq 0.001$), high dose group ($p = 0.011$), and high-dose maintenance infusion ($p \leq 0.001$) when compared to the placebo group. There was no difference between placebo and low dose group ($p = 0.555$). It was also less in LM group, where maintenance infusions were used in comparison to groups L ($p = 0.034$) and H ($p = 0.227$) without it. The HM group patients also had a significant p-value less than group L ($p \leq 0.001$) and group H ($p = 0.023$) There was no difference between low and high doses of a single infusion of tranexamic acid ($p = 0.059$). There was a significant difference in blood loss when maintenance infusion was used with a high-dose when compared to the high dose group ($p = 0.002$). There was also no difference between groups LM and HM ($p = 0.076$), indicating low dose of tranexamic acid with a maintenance infusion as the ideal regimen in reducing intraoperative blood loss. The results were given in Table 3.

The reduction in postoperative blood loss in the drain for first 24 hours was 80 ± 44.44 mL in the placebo group, 89.88 ± 44.87 mL in the low-dose group, 56.7 ± 29.12 mL in the low-dose plus maintenance group, 77.9 ± 35.74 mL in the high-dose group and 46.7 ± 19.9 mL in the high-dose maintenance group. The p-value was < 0.001 and it was statistically highly significant. The postoperative blood loss in the drains was significant in groups LM ($p = 0.006$) and HM ($p \leq 0.001$) than the placebo group. There was no difference in groups L ($p = 0.325$) and H ($p = 0.826$) compared to the placebo group. The postoperative blood loss was significantly less in groups LM ($p \leq 0.001$) and HM ($p \leq 0.001$) than in L group. There was no significant reduction between groups LM and HM ($p = 0.076$). It was significantly less in groups LM ($p = 0.004$)

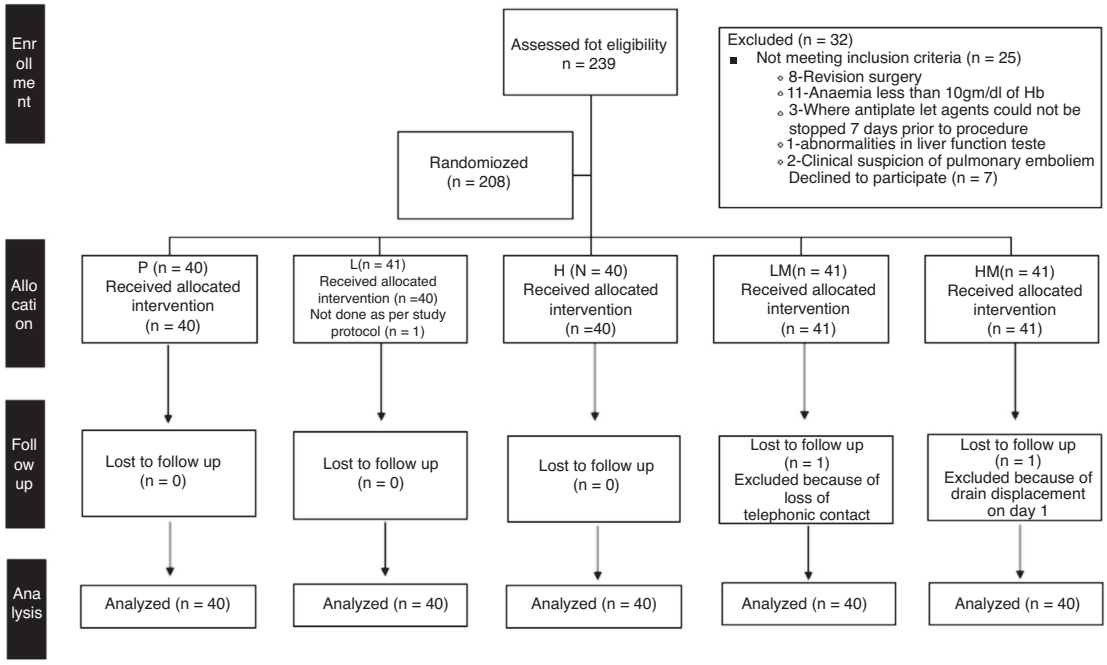

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

Table 1 Demographic characteristics and Hemoglobin concentration.

	Group P	Group L	Group LM	Group H	Group HM	*p*-value
Age (years)	51.15 (15.4)	53.7 (16.72)	52.8 (15.9)	53.32 (19.99)	51 (15.4)	0.927[a]
Weight (kg)	58.8 (2.5)	57.3 (5.84)	59.25 (6)	57.7 (9.9)	59.6 (5.6)	0.441[a]
Sex (M/F)	25/15	26/14	22/18	20/20	21/19	0.603[a]
Duration of surgery (minutes)	151.25 (55.15)	148.25 (53.91)	135.8 (44.7)	161.6 (49.6)	139.7 (34.3)	0.136[a]
Preoperative Hemoglobin ($g\,dL^{-1}$)	11.19 (1.12)	11.6 (1.26)	11.7 (1.1)	11.52 (1.1)	11.4 (0.89)	0.267[a]
Postop day 4 Hemoglobin ($g\,dL^{-1}$)	10.59 (0.989)	10.86 (1.20)	10.84 (1.15)	10.7 (1.03)	10.4 (1.75)	0.453[a]

[a] *p*-value not significant.
Values are in mean (standard deviation).
Using Chi-Square test for sex and ANOVA for the others.

Table 2 Type of surgery.

Type of surgery	Group P	Group L	Group LM	Group H	Group HM	*p*-value
Spine instrumentation	18 (45%)	16 (40%)	19 (47.5%)	22 (55%)	20 (50%)	
Total hip replacement	9 (22.5%)	10 (25%)	7 (17.5%)	7 (17.5%)	9 (22.5%)	0.999[a]
Femur fracture fixation	13 (32.5%)	14 (35%)	17 (42.5%)	11 (27.5%)	11 (27.5%)	

[a] *p*-value not significant.
Values are in number of patients (percentage of patients).

and HM ($p \leq 0.001$) than in H group. The results were given in Table 4.

The mean transfusion requirements were expressed as number of packed RBCs transfused: it was 31 units in the placebo group, 27 units in the low-dose group, 17 units in the high-dose group and nine units in low-dose plus maintenance and high-dose maintenance groups. The transfusion requirements were significantly less in groups LM ($p \leq 0.001$) and HM ($p \leq 0.001$) than placebo group. There was no difference in groups L ($p = 0.62$) and H ($p = 0.06$) and the placebo group. Compared to L group, there was no difference with H group ($p = 0.62$) but there was statistically significant reduction in groups LM ($p = 0.021$) and HM ($p = 0.02$). There was no difference between groups LM and H ($p = 3.13$), groups HM and H ($p \leq 0.001$), groups LM and HM ($p = 0.92$). The results were tabulated in Table 5. There was no case of DVT or any thrombotic complications reported during the study.

Discussion

Tranexamic acid is a synthetic analogue of the amino acid lysine (4-aminoethyl cyclohexane carboxylic acid) and

Table 3 Intraoperative blood loss among groups.

	Group P	Group L	Group LM	Group H	Group HM	*p*-value
Mean (SD) mL	440 (207.54)	412.5 (208.21)	290 (149.6)	332.5 (162.33)	240.7 (88.15)	< 0.001[a]
p-value (Intergroup comparisons)						
Group L	0.556[b]					
Group LM	< 0.001[a]	0.003[a]				
Group H	0.0118[a]	0.059[b]	0.227[b]			
Group HM	< 0.001[a]	< 0.001[a]	0.076[b]	0.002[a]		

[a] *p*-value significant.
[b] *p*-value not significant.
Values are in mean (standard deviation).
Using ANOVA for comparison among groups: using Scheffe's test for pairwise comparisons.

Table 4 Postoperative blood loss in drain in 24 hrs.

	Group P	Group L	Group LM	Group H	Group HM	*p*-value
Mean (SD) mL	80 (44.44)	89.88 (44.87)	56.7 (29.12)	77.9 (35.74)	46.7 (19.9)	0.001[a]
p-value (Intergroup comparisons)						
Group L	0.325[b]					
Group LM	0.006[a]	< 0.001[a]				
Group H	0.816[b]	0.19[b]	0.004[a]			
Group HM	< 0.001[a]	< 0.001[a]	0.076[b]	< 0.001[a]		

[a] *p*-value significant.
[b] *p*-value not significant.
Values are in mean (standard deviation).
Using ANOVA for comparison among groups: using Scheffe's test for pairwise comparisons.

Table 5 Mean transfusion requirements.

	Group P	Group L	Group LM	Group H	Group HM	*p*-value
Mean (SD) RBC packs	31 (77.5%)	27 (67.5%)	9 (22.5%)	17 (42.5%)	9 (22.5%)	0.001[a]
p-value (Intergroup comparisons)						
Group L	0.62[b]					
Group LM	0.001[a]	0.021[a]				
Group H	0.06[b]	0.62[b]	3.13[b]			
Group HM	0.001[b]	0.02[a]	4.51[b]	0.92[b]		

[a] *p*-value significant.
[b] *p*-value not significant.
Values are in number of pRBC transfused (percentage of patients).
Using ANOVA for comparison among groups: using Scheffe's test for pairwise comparisons.

exerts its anti-fibrinolytic effects by blocking lysine-binding sites on plasminogen, thus preventing its conversion to plasmin.[6,7] The use of tranexamic acid in orthopedic surgeries is appealing because of its ability to penetrate joint spaces.[8] Tranexamic acid has also been used in neurosurgery, cardiovascular and maxillofacial surgeries.[9–12] Though several studies have been published regarding the use of tranexamic acid in hip fracture, replacement and spine surgeries, the ideal dosing regimen is not proven.[13–15] We performed this double-blinded, randomized study to compare four different dosing regimens (low dose bolus only, low dose bolus with maintenance, high dose bolus only, and high dose bolus with maintenance) with the placebo for a reduction in intraoperative blood loss, postoperative drain collection, and blood transfusion.

There was no significant difference in preoperative hemoglobin and hemoglobin on the fourth postoperative day between the groups. This implies that the replacement of blood products was identical in all the groups. The intraoperative blood loss and postoperative blood loss in drains in 24 hours were significantly less in both the groups where maintenance infusions were used (groups LM, HM). There was no significant reduction in blood loss when higher doses were used indicating that higher doses were not necessary. McHugh et al. compared low dose (15 mg kg^{-1} loading dose followed by infusion of 6 mg kg^{-1} h^{-1} until the end of surgery along with 1 mg kg^{-1} priming dose in the bypass circuit) and high dose (30 mg kg^{-1} loading dose followed by infusion of 15 mg kg^{-1} h^{-1} until the end of the surgery along with 2 mg kg^{-1} priming dose in the bypass circuit) tranex-

amic acid protocol for coronary artery bypass graft (CABG).[6] They concluded that low-dose TA protocol is as effective as a high-dose protocol for anti-fibrinolysis in patients undergoing primary CABG.

Aytuluk et al. studied the effectiveness of TA in lower doses with infusion in Total Knee Arthroplasty (TKA). They concluded that a total dose of 10 mg kg^{-1} of TA intravenous infusion starting 15 minutes before the surgery until wound closure can significantly decrease total blood loss and the intraoperative infusion regimen is more effective than the divided-dose regimen.[3] Maniar et al. studied different dosages, timings, and modes of administration to define the most effective regimen of tranexamic acid in achieving a maximum reduction of blood loss in TKA. They observed that TA was most effective when it is administered preoperatively, intraoperatively and postoperatively in a reduction in drain loss as well as total blood loss.[5]

Thipparampall et al. concluded that a bolus of TA (10 mg kg^{-1}) followed by infusion (1 mg kg^{-1} h^{-1}) is more useful than a single dose in decreasing perioperative blood loss in patients undergoing hip surgeries. It reduces the transfusion of blood products without increasing the risk of thromboembolic events.[8] Zufferey et al. studied whether the addition of IV infusion to bolus dose was more effective in reducing blood loss in primary hip arthroplasty and concluded that supplementary perioperative administration of TA did not achieve any further reduction in blood loss.[3]

The mean transfusion requirements were also less in groups LM and HM, with no difference between them. The main risk associated with the use of TA is the high incidence of thrombotic complications. All the patients were followed for six weeks by the telephonic interview. No complications were reported in any of the cases. Ker et al. performed a systematic review and cumulative meta-analysis on the effect of tranexamic acid on surgical bleeding. They included 129 trials, totalling 10,488 patients, carried out between 1972 and 2011. The risk ratios for different thrombotic complications reported with the use of TA were as follows: myocardial infarction – 0.68, stroke – 1.14, deep vein thrombosis – 0.86, and pulmonary embolism – 0.61. They concluded that the effect of tranexamic acid on thromboembolic events and mortality remains uncertain implying no direct documented risk. It is imperative for the patients to be made aware of this evidence so that they can make an informed choice.

The first limitation is the accuracy of blood loss estimation. The blood loss was estimated by measuring the weight of gauzes and pads, collection in the suction bottle, and clinical assessment of the surgical field. Though this method gives a fair estimate, it may not be accurate. However, the blood transfusion was not done as per blood loss estimation but by hourly hematocrit measurement. The hematocrit measurement can also be affected by hemodilution depending on the volume of crystalloids administered, which was not standardized. The second limitation is that we included three different types of major orthopedic procedures which will have different blood loss and operated by three different surgeons. Since we wanted the benefits of TA to be utilized for all patients, we included all major orthopedic procedures being done in our hospital. We also ensured that all spine instrumentation was done by the first surgeon, THR by a second surgeon and femur fracture internal fixation was done by the third surgeon. There was no statistical difference in the type of surgeries between the groups. We did not include TKA as the use of tourniquets in only a few patients in a group will create a bias in the study. Thirdly, the cost-benefit analysis was not done in our study. Fourth, we followed up the patients for only up to six weeks. The long-term follow-up could not be done due to practical difficulties.

To conclude, tranexamic acid was effective in reducing perioperative blood loss and transfusion requirements in major orthopedic surgeries. The reduction was significant when maintenance infusion was used along with a bolus dose. There was no added benefit when higher doses were used. Hence, we recommend a bolus dose of 10 mg kg^{-1} with a maintenance infusion of 1 mg kg^{-1} h^{-1} until the end of surgery. The thrombotic complications were not encountered in our study.

Conflicts of interest

The authors declare no conflicts of interest.

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