The Role of Tranexamic Acid in the Prevention and Management of Blood Loss in Total Joint Arthroplasty*

O papel do ácido tranexâmico na prevenção e gerenciamento da perda de sangue na artroplastia total de articulação

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Rev Bras Ortop 2022;57(3):415–421.

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Abstract

Objective To collect data on the role played by tranexamic acid in the prevention and management of blood loss in patients undergoing total hip arthroplasty and total knee arthroplasty.

Methods In the present prospective, comparative study, 30 patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA) were randomly allocated into 1 of 2 groups with 15 patients each. Tranexamic acid was administered by intravenous and topical routes in the study group, but it was not administered in the control group. Preoperative blood parameters, intraoperative and postoperative blood loss, and need for blood transfusion were noted. Statistical analysis was performed using the chi-squared test and the independent *t*-test.

Results The study group had statistically significant higher postoperative hemoglobin values ($p = 0.03$), less difference between pre and postoperative hemoglobin value ($p = 0.046$), less difference between pre and postoperative packed-cell volume ($p = 0.06$), less intraoperative measured blood loss ($p = 0.015$), and less volume of blood collected in the drain ($p = 0.0291$) compared with the control group. There was also reduced frequency of blood transfusions in the study group ($p = 0.0008$).

Conclusion Tranexamic acid is associated with reduced intra and postoperative blood loss and reduced frequency of blood transfusions in patients undergoing THA/TKA.

Keywords
- blood loss, surgical
- blood transfusion
- arthroplasty, replacement, hip
- knee
- tranexamic acid

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received
June 13, 2020
accepted
December 17, 2020
published online
October 25, 2021

DOI https://doi.org/10.1055/s-0041-1729933.
ISSN 0102-3616.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

Objetivo Coletar dados sobre o papel desempenhado pelo ácido tranexâmico na prevenção e gerenciamento da perda de sangue em pacientes submetidos à artroplastia total do quadril (ATQ) e à artroplastia total do joelho (ATJ).

Métodos Neste estudo prospectivo e comparativo, 30 pacientes submetidos à ATQ ou à ATJ foram alocados aleatoriamente em 1 de 2 grupos com 15 pacientes. O ácido tranexâmico foi administrado por rotas intravenosas e tópicas no grupo de intervenção, mas não foi administrado no grupo controle. Foram observados parâmetros sanguíneos pré-operatórios, perda de sangue intra- e pós-operatória e necessidade de transfusão de sangue. A análise estatística foi realizada utilizando-se teste do qui-quadrado e o teste-t independente.

Resultados O grupo de intervenção apresentou hemoglobina mais elevada no pós-operatório de forma estatisticamente significante ($p = 0,03$), menor diferença entre concentração de hemoglobina pré- e pós-operatória ($p = 0,046$), menor diferença entre volume de células embaladas pré- e pós-operatório ($p = 0,06$), menor perda de sangue intraoperatória medida ($p = 0,015$) e menor volume de sangue coletado na drenagem ($p = 0,0291$) em comparação com o grupo controle. Também houve redução da frequência de transfusões de sangue no grupo de intervenção ($p = 0,0008$).

Conclusão O ácido tranexâmico está associado à redução da perda sanguínea intraoperatória e pós-operatória e à redução da frequência de transfusões de sangue em pacientes submetidos à ATQ/ATJ.

Palavras-chave

- perda sanguínea cirúrgica
- transfusão de sangue
- artroplastia de quadril
- joelho
- ácido tranexâmico

Introduction

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) have become increasingly popular procedures in the treatment of painful arthritis. Both procedures are associated with substantial blood loss leading to anemia and need for blood transfusion. "Postoperative anemia predisposes the patient to increased risk of cardiovascular events and postoperative infection besides increasing the length of hospital stay and hospital costs."[1] Blood transfusions are associated with risks such as transmission of blood-borne diseases, hemolytic reactions, circulatory overload, acute lung injury, and coagulopathy.

This has led to the evolution of multimodal blood conservation programs designed to stimulate erythropoiesis, maintain hemostasis, and minimize blood loss to optimize the patient's hemoglobin concentration, reduce blood transfusions, and improve the final outcome.

Increased fibrinolysis is a proven cause for blood loss during THAs and TKAs.[2] Hence, tranexamic acid, an antifibrinolytic agent is a promising pharmacological option for reducing blood loss. However, there is no single, established, standardized protocol for tranexamic acid administration in THAs and TKAs.

The objective of the present study was to collect data on the role played by tranexamic acid in the prevention and management of blood loss in patients undergoing THAs and TKAs.

Methods

The present study was performed in compliance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects after approval by the institutional review board.

In this prospective comparative study conducted at the department of orthopedics in a tertiary care hospital, the sample size was calculated using the formula:

$n = z^2pq/d^2$

Where n = sample size

z = standard normal deviate set at 1.96 corresponding to 95% confidence level

p = proportion of study population undergoing THA and TKA

q = 1-p

d = degree of accuracy set at 0.05

The sampling technique followed was simple computerized random sampling. All patients, male and female of all age groups undergoing THA or TKA during the study period were included. Written, informed consent was obtained. Patients with history of arterial or venous thrombosis, intrinsic risk of thromboembolic events, anemia, acute renal failure, history of seizures, allergy to tranexamic acid as well as patients not consenting to the study were excluded. The sample population of 30 was then randomly divided into 2 groups (study and control) of 15 each. The study group received both intravenous and topical tranexamic acid, and the control group did not receive tranexamic acid. The findings were then computed and compared between the groups: THA study and THA control, and TKA study and TKA control groups.

Preoperative assessment included the patient's age, gender, weight, height, and body mass index (BMI), presence of comorbidities, estimation of hemoglobin concentration,

packed-cell volume (PCV), platelet count, and PT/INR (Prothrombin Time/International Normalized Ratio) values.

Intraoperatively, tranexamic acid was administered intravenously (1 g in 100 mL of saline prior to incision in THA and prior to tourniquet inflation in TKA); the amounts of irrigation fluid used and of suctioned fluid collected were documented; serial blood pressure (BP) monitoring was performed; and topical tranexamic acid (1 g) was administered locally all around the cemented joint (left in place for 5 minutes before wound closure in THA and for 15 minutes before tourniquet deflation in TKA). The duration of the surgery was noted, blood-soaked wet swabs were collected immediately, and their weight was measured. The weight was compared with the weight of the same number of dry swabs.

Postoperatively, hemoglobin and, PCV values at 24 hours postsurgery, drain collection at 48 hours postsurgery, and blood transfusions were documented. Any adverse events that occurred during the patient's hospital stay as well as the duration of hospital stay were noted.

The allowable blood loss (ABL) was calculated for each patient

ABL = [EBV x (Hi - Hf)] / Hi

ABL = allowable blood loss
EBV = estimated blood volume
Hi = initial hemoglobin
Hf = final hemoglobin (standard level of hemoglobin set in each hospital according to their operating protocols. The level set in the present study was 10 g/dL. Blood was transfused if the patient's postoperative hemoglobin concentration fell below 10 g/dL).
EBV = body weight (kg) x average blood volume (ml/kg). (average blood volume: adult men: 75 ml/kg; adult women: 65 ml/kg)

The intraoperative measured blood loss (MBL) was calculated for each patient

MBL = (volume of suction fluid + volume of blood in swabs) subtracted by the volume of irrigation fluid

Volume of blood in swabs = weight of wet swabs – weight of dry swabs (taking 1 ml of blood as equivalent to 1 g of weight)

The difference between pre and postoperative hemoglobin concentration and pre- and postoperative PCV was calculated.

Statistical analysis was performed using the IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA).

Frequency was calculated for categorical variables: gender, presence of comorbidities, BP in mm Hg, procedure performed, need for blood transfusion.

Descriptive statistics (minimum, maximum, mean, and standard deviation) were calculated for continuous variables: age (years), BMI (kg/m^2), surgery duration (hours), duration of hospital stay (days), postoperative hemoglobin value, postoperative PCV, difference between pre and postoperative hemoglobin value and pre and postoperative PCV, allowable blood loss (ml), volume of blood in swabs (ml), measured blood loss (ml), volume of blood in drain (ml).

The independent *t*-test was performed to compare the means of the two groups with respect to measured blood loss, volume of blood in swabs, and duration of hospital stay. The Pearson chi-squared test was used to determine the difference between the two groups with respect to need for blood transfusion. The p-value considered for statistical significance was < 0.05, with a confidence interval of 95%.

Results

As illustrated in ►**Fig. 1**, there was equal distribution of males and females (15 males, 15 females) in the sample population. A total of 66.6% had normal BMI, and 33.3% were overweight. The number of patients with comorbidities (diabetes and/or hypertension) were 7 in the control group and 2 in the subject group. Sixteen patients underwent THA, and 14 patients underwent TKA. The mean age of the sample population was 53 years. As illustrated in ►**Fig. 2**, the mean duration of hospital stay was longer in the control group compared with the study group, that is 12 days and 10 days, respectively.

The mean postoperative hemoglobin concentration was significantly higher in the subject group than in the control group, that is 11.91 and 10.53, respectively ($p = 0.03$), as shown in ►**Fig. 3**. The mean postoperative hemoglobin concentration in THA cases was higher in the study group than that in control group, that is 11.17 and 10.7, respectively ($p = 0.67$). The mean postoperative hemoglobin concentration in TKA was higher in the study group than that in the control group, that is 12.65 and 10.34, respectively ($p = 0.002$).

The mean difference between pre and postoperative hemoglobin concentration was significantly lower in the study group compared with control group, that is 1.4 and 2.09, respectively ($p = 0.046$), as shown in ►**Fig. 4**.

The mean postoperative PCV was higher in the study group than that in control group, that is 35.07 and 32.56, respectively, although this is statistically insignificant ($p = 0.15$). The mean postoperative PCV in THA cases higher in the study group compared with the control group, that is 33.78 and 33.25, respectively ($p = 0.85$). The mean postoperative PCV in TKA cases was higher in the study group than that in the control group, that is 36.2 and 31.77, respectively ($p = 0.03$).

The mean difference between pre and postoperative PCV was lower in the study group compared with control group, that is 4.30 and 6.59, respectively ($p = 0.06$), as illustrated in ►**Fig. 5**.

The mean allowable blood loss in the study group was 1,059.31 ml and 926.35 ml in the control group. The mean volume of blood in swabs was 483.33 ml and 565.4 ml in the study and control groups, respectively. The volume of the blood in swabs did not differ significantly between the 2 groups ($p = 0.32$).

As shown in ►**Table 1**, the mean intraoperative MBL in the study group was 291 ml, which was significantly less than that in the control group which was 493.33 ml ($p = 0.0015$). The mean MBL in THA cases was significantly less in the study

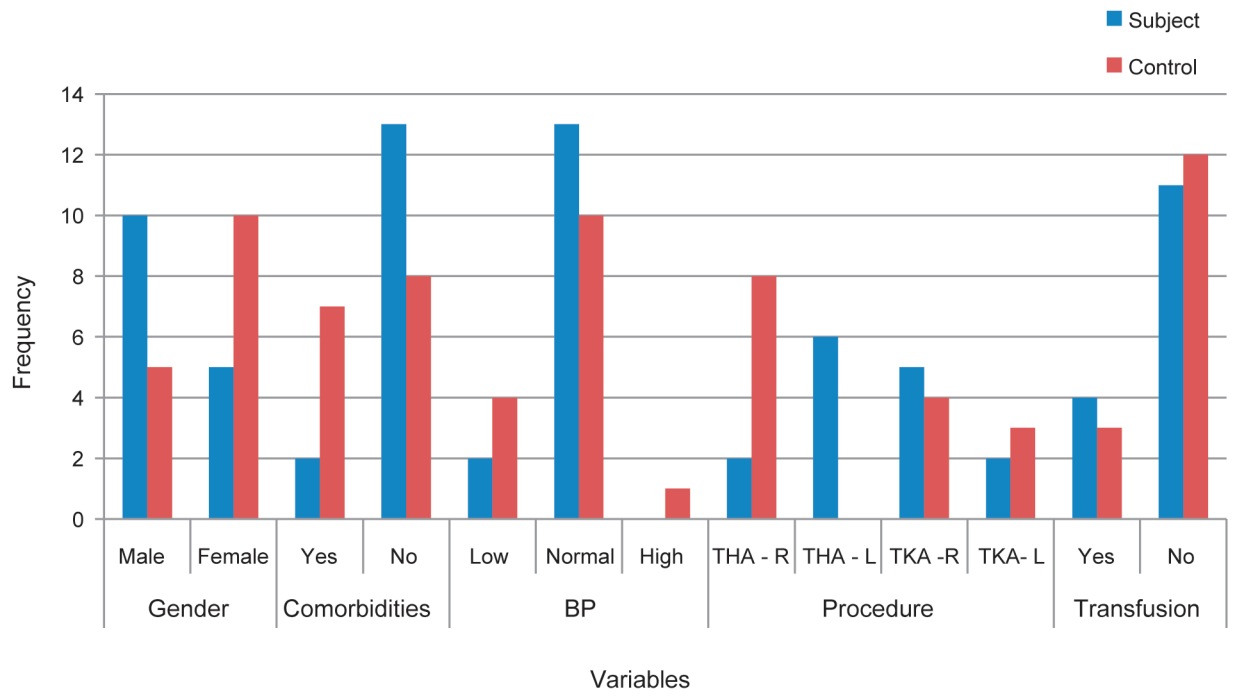

Fig. 1 Frequency distribution according to gender, comorbidities, blood pressure, procedure, and blood transfusion.

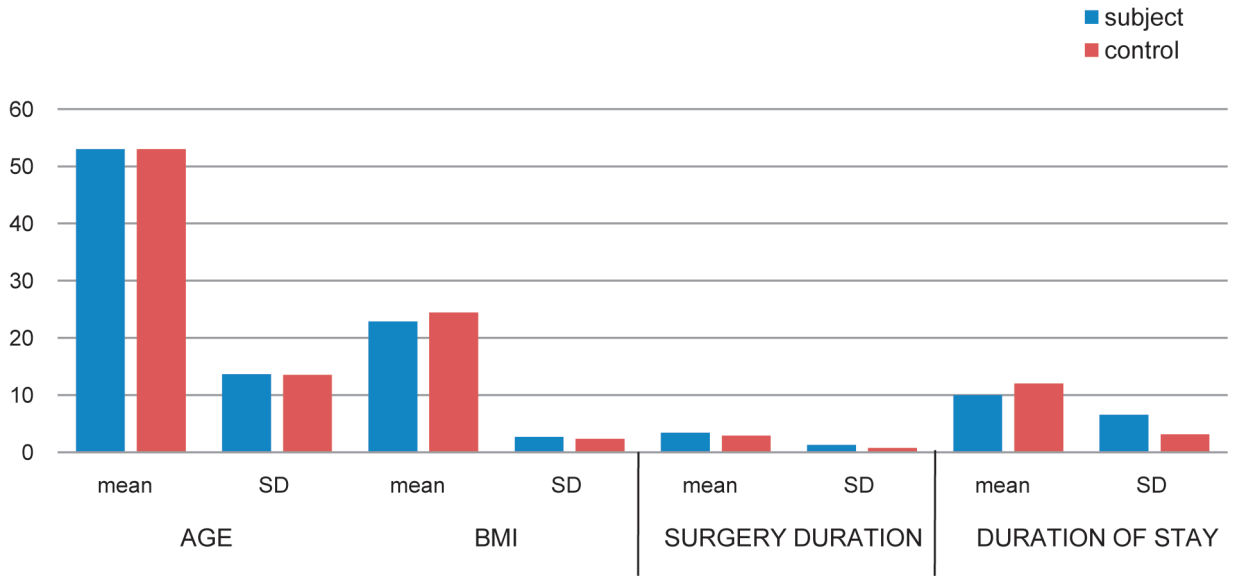

Fig. 2 Descriptive statistics for age, body mass index, surgery duration, duration of hospital stay.

group compared with the control group, that is 311.7 ml and 566.8 ml, respectively ($p = 0.01$). The mean MBL in TKA cases was less in subject compared with control group that is 272.8 ml and 409.2 ml respectively ($p = 0.11$).

The mean volume of blood collected in the drain postoperatively in the study group was 496.66 ml, which was significantly less than that in control group, which was 686.66 ml ($p = 0.0291$), as illustrated in ►**Fig. 6**. The mean volume of blood in the drain postoperatively in THA cases was lower in the study group than in the control group, 407.14 ml and 650 ml, respectively ($p = 0.05$). The mean volume of blood collected in the drain postoperatively in TKA cases was lower in the study group than in the control group, 575 ml and 728.57 ml, respectively ($p = 0.21$).

In the study group, 1 patient required blood transfusion (THA), whereas in the control group, 3 patients required blood transfusion (THA). This is a statistically significant difference, and the p-value was calculated with the chi-squared test (0.0008), as illustrated in ►**Fig. 7**.

There were no complications or adverse events in the intra and postoperative periods following tranexamic acid administration in both the groups.

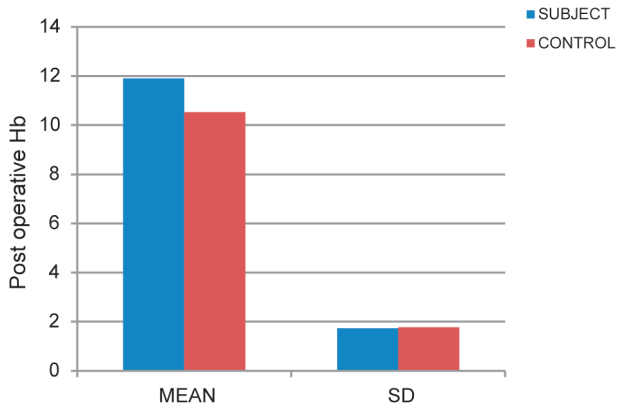

Fig. 3 Postoperative hemoglobin.

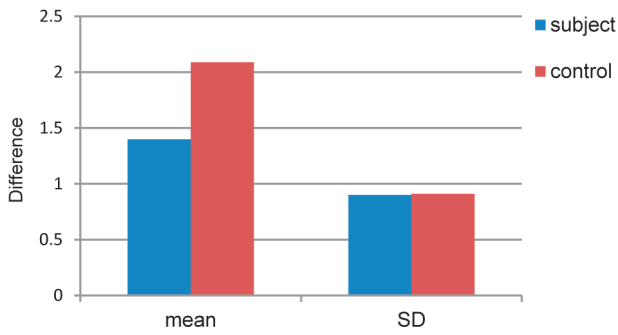

Fig. 4 Difference between preoperative and postoperative hemoglobin.

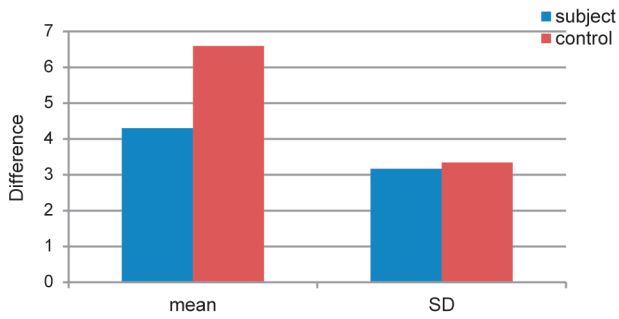

Fig. 5 Difference between preoperative and postoperative packed cell volume.

Table 1 Intraoperative measured blood loss

MBL	Study	Control
Mean	754.33 ml	810 ml
SD	684.33 ml	556.06 ml
THA		
Mean	311.7 ml	566.8 ml
TKA		
Mean	272.8 ml	409.2 ml

Abbreviations: MBL, measured blood loss; SD, standard deviation; THA, total hip arthroplasty; TKA, total knee arthroplasty.

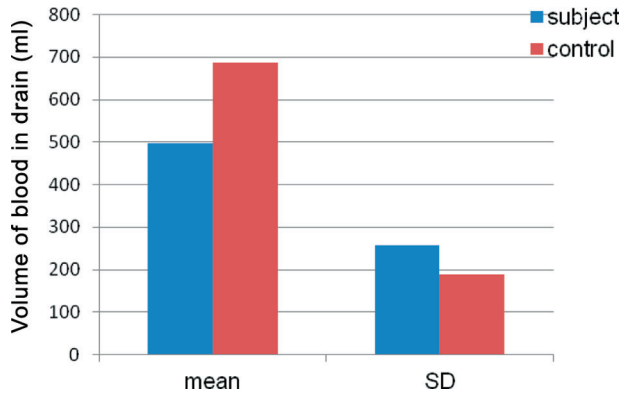

Fig. 6 Volume of blood in drain.

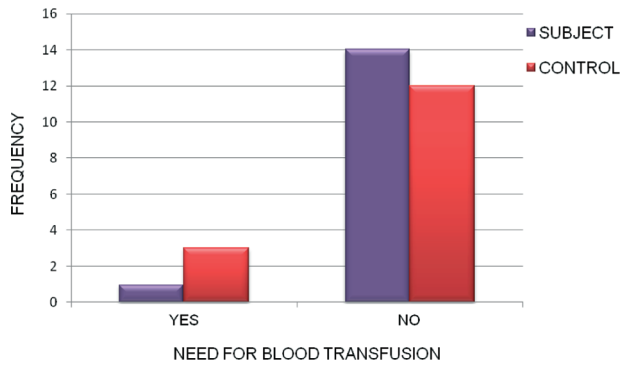

Fig. 7 Frequency of blood transfusion.

Discussion

With the advent of modern implants and instrumentation, THAs and TKAs have become viable, efficient options for the treatment of painful arthritis. These procedures are associated with substantial blood loss. Hence, implementing an efficient blood conservation program is essential. Tranexamic acid is an antifibrinolytic that has been proved by many studies and trials in the literature to be a safe and efficient option for the control of blood loss in THAs and TKAs.

According to a study conducted by Huang et al.,[3] there is a lot of ambiguity among studies with respect to administration protocols for tranexamic acid.

Alvarez et al.[4] and Alshryda et al.[5] found that intravenous administration of tranexamic acid significantly reduces the blood loss in arthroplasty. The effects of topical administration of tranexamic acid were studied by Chimento et al.,[6] Panteli et al.,[7] and Zekcer et al.[8] The results showed significant reduction in blood loss. The effect of tranexamic acid administered through both intravenous and topical routes was studied by Wu et al.,[9] Imai et al.,[10] and Gandhi et al.,[11] and they found a significant reduction in blood loss. A metanalysis conducted by Liu et al.[12] of six randomized control trials also concluded the same.

In the present literature, there is no consensus regarding the standard protocol of administration, be it the dose or the route of administration. Besides, each of the studies have investigated a different set of blood loss parameters. The present study combined both intravenous and topical routes of administration of tranexamic acid in THA and TKA cases. Various parameters of blood loss, both intra and postoperative were combined and assessed. This study concluded that tranexamic acid administration is associated with statistically significant higher postoperative hemoglobin, less difference in pre and postoperative hemoglobin concentration and PCV, less intraoperative measured blood loss, and less volume of blood in the drain postoperatively.

Some studies have assessed the various factors that might affect blood loss. According to Huang et al.,[3] tourniquet use in TKA is associated with less intraoperative blood loss but leads to increased postoperative blood loss. Poeran et al.[13] stated in their study that tourniquet use in TKA induces fibrinolysis and, hence, increases blood loss. Aaron Larson et al.[14] stated that there are no methods to assess the volume of the blood that is not suctioned through the suction tube during surgery. They also found that increased requirement of IV fluids during or after a procedure may have lowered hemoglobin and/or PCV levels by dilution.

The need for a blood transfusion postoperatively depended on many factors, as analyzed by some studies. According to a study by Pola et al.,[15] patients undergoing arthroplasty were at a higher risk of needing a blood transfusion if they were hypertensive. Another study by Marchant et al.[16] found that blood transfusion requirement was higher when the patient was diabetic. Studies performed by Aderinto et al.[17] and Carling et al.[18] found that the need for blood transfusion depended mainly on the preoperative hemoglobin concentration of that patient. Singh et al.[19] and Zhang et al.[20] also found that the most reliable indicator of need for blood transfusion is the preoperative hemoglobin level.

In the present study, in the study group, 1 patient required blood transfusion (THA case), whereas in the control group, 3 patients required blood transfusion (THA cases). This is a statistically significant difference. Finally, the mean duration of hospital stay was longer in the control group compared with the subject group, that is 12 days and 10 days, respectively.

Andrea et al.[21] stated that there is a risk of thromboembolic events and proinflammatory effects of tranexamic acid administration. They stated that tranexamic acid-lysine residues are not specific to decreasing blood loss but are also a part of other metabolic and signaling pathways, protein–protein interactions and posttranslational modifications. Thus, without established evidence of hyperfibrinolysis, there is no justification for tranexamic acid use.

However, there were no complications or adverse events in the intraoperative and postoperative periods in both the subject and control groups in this study.

The limitations of the present study were that its sample size was relatively small and that the miscellaneous blood loss (due to spillage onto floor, gowns, drapes) was not included. More studies need to be performed to assess the relationship between blood loss, tranexamic acid, and tourniquet application in TKA. Studies assessing the effect of tranexamic acid on the coagulation profile, pharmacodynamics in the elderly, diabetics, patients with hypertension, altered renal, and liver function need to be conducted on a large scale to adequately establish the safety of tranexamic acid. Large scale multicenter studies are necessary to establish protocols about standard dosage, subsequent doses after a bolus dose, and a route of administration that is safe, efficient, and cost effective.

Conclusion

The present study concludes that tranexamic acid administration is associated with higher postoperative hemoglobin, less difference between pre and postoperative hemoglobin concentration and packed-cell volume, less intraoperative measured blood loss, and less collection of blood in the drain in patients undergoing THA or TKA.

Thus, tranexamic acid is associated with reduced intra and postoperative blood loss, and, ultimately, reduced frequency of blood transfusions in patients undergoing THA or TKA.

Financial Support
There was no financial support from public, commercial, or non-profit sources.

Conflict of Interests
The authors have no conflict of interests to declare.

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