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ORIGINAL ARTICLE

ASSESSMENT OF THE USE OF TRANEXAMIC ACID AFTER TOTAL KNEE ARTHROPLASTY

AVALIAÇÃO DO USO DO ÁCIDO TRANEXÂMICO DURANTE A ARTROPLASTIA TOTAL DO JOELHO

Chilan Bou Ghosson Leite[1], *Lucas Verissimo Ranzoni*[1], *Pedro Nogueira Giglio*[1], *Marcelo Batista Bonadio*[1], *Lucas da Ponte Melo*[1], *Marco Kawamura Demange*[1], *Riccardo Gomes Gobbi*[1]

1. Universidade de São Paulo, Faculdade de Medicina, Department of Orthopedics and Traumatology, São Paulo, SP, Brazil.

ABSTRACT

Objective: To evaluate the profile of blood loss and blood transfusions after the introduction of Tranexamic acid (TXA) in a tertiary university hospital in Brazil. Methods: 173 patients were retrospectively divided into two groups: the ones who received TXA and the control group. Hemoglobin levels (Hb), drain output, transfusion rates, and thromboembolic events were measured. Results: Among the patients included in this study, 82 cases received TXA. Blood transfusion occurred in 3 cases of the TXA group (3.7%), and in 27 control group cases (29.7%; $p < 0.001$). The average Hb decrease was 2.7 g/dl (± 1.39) and the median drain output was 270 mL in the TXA group. In the control group, the values were 3.41 g/dl (± 1.34; $p < 0.001$) and 460 mL ($p < 0.001$), respectively. Thromboembolic events occurred in 2 TXA group cases (2.4%) and in 3 control group cases (3.3%; $p > 0.999$). Conclusion: TXA was effective in reducing blood transfusion rates, Hb decrease, and drain output on the 1st postoperative day without increasing thromboembolic events. ***Level of evidence III, Retrospective comparative study.***

Keywords: Tranexamic Acid. Blood Transfusion. Knee Replacement Arthroplasty.

RESUMO

Objetivo: Avaliar o perfil de perda sanguínea e hemotransfusões após a introdução da prática do uso de ácido tranexâmico (ATX) em um serviço terciário universitário brasileiro. Métodos: 173 pacientes foram separados retrospectivamente em dois grupos: uso do ATX e controle. Foram analisados valores da hemoglobina (Hb), débito do dreno, necessidade transfusional e complicações tromboembólicas. Resultados: Dentre os pacientes admitidos no estudo, 82 fizeram uso do ATX. Hemotransfusão ocorreu em 3 casos do grupo ATX (3,7%) e em 27 controles (29,7%, $p < 0,001$). A queda de Hb teve média de 2,7 g/dl (± 1,39) e o débito do dreno, mediana de 270 ml no grupo ATX. No grupo controle, os valores foram de 3,41 g/dl (± 1,34; $p < 0.001$) e de 460 ml ($p < 0.001$), respectivamente. Eventos tromboembólicos ocorreram em 2 casos (2,4%) no grupo ATX e em 3 no controle (3,3%, $p > 0.999$). Conclusão: o uso do ATX foi efetivo em reduzir hemotransfusões, queda de Hb e débito drenado no 1° dia pós-operatório, sem aumentar eventos tromboembólicos. ***Nível de evidência III, Estudo retrospectivo comparativo.***

Descritores: *Ácido Tranexâmico. Transfusão de Sangue. Artroplastia do Joelho.*

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INTRODUCTION

Total knee arthroplasty (TKA) is currently one of the most cost-effective treatments in the management of osteoarthrosis in more advanced stages.[1] Patients undergoing TKA are in risk for blood losses over 1500 ml, being submitted to allogenic blood transfusion in 10%-38% of the cases.[2] Allogenic blood transfusion is not a benign procedure and is associated with complications, such as transmission of infectious diseases, transfusion reactions, fluid overload, and periprosthetic infection.[3] In addition, it can lead to prolonged hospital stay, thromboembolic events, and increased in-hospital mortality.[4] Different strategies have been used to reduce blood loss after TKA, such as autologous transfusion, cell saver, pneumatic tourniquet, and the use of tranexamic acid (TXA).[1,5] The fibrinolytic process is a major cause of intraoperative bleeding.[3] By acting with the inhibition of hyperfibrinolysis, TXA stabilizes the fibrin clot and reduces blood losses. Mechanistically, it is a competitive inhibitor of plasminogen-activating enzymes, preventing its proteolytic activity to avoid the formation of plasmin and the

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Correspondence: Chilan Bou Ghosson Leite. Rua Ovídeo Pires de Campos, 333, Cerqueira Cesar, São Paulo, SP, Brazil, 01246000. chilanleite@gmail.com

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consequent degradation of fibrin.[1,6] Several systematic reviews and meta-analyses have demonstrated the TXA role, in cases of TKA, in reducing blood loss and transfusion needs, without increasing the risk of thromboembolic events.[6-8]

TXA is usually indicated to prevent and treat different causes of bleeding, including large surgical procedures, such as orthopedic, cardiac, and liver transplantation surgeries. In this regard, TXA reduces the need for blood transfusion improving the patient's outcome, therefore its use in polytraumatized patients may decrease mortality by preventing the excessive bleeding.[9]

In recent years, the use of TXA has increased progressively in the TKA worldwide centers . On the other hand, the impact of TXA after TKA is still poorly documented in Brazil. Our service started to use this medication in 2013, introducing the administration of TXA routinely by the end of 2014. Therefore, we could gather a significant amount of experience.

This study aims to evaluate the impact of the TXA routine use, reducing blood loss related to the primary TKA procedure. The study aims to evaluate the hematimetric parameters, the number of transfusions, and the drain output in a retrospective cohort of patients admitted in a tertiary university hospital in Brazil.

MATERIALS AND METHODS

The study was approved by our ethics committee (CAPPesq number 15754619.7.0000.0068). All patients signed an informed consent form. A retrospective cohort study was carried out with patients undergoing TKA between 2013 and 2017 admitted in our service.

Patients were not included in the study if they had:

- any hematological diseases, renal insufficiency, hepatic insufficiency, previous cardiovascular and/or thromboembolic events;
- preoperative use of anticoagulant or other medications that alter coagulation;
- alteration in coagulation exams prior to the surgical procedure;
- intraoperative fracture that required the use of intramedullary nails and revision components.

Based on that, 220 patients were selected. Of those, 47 were excluded due to the lack of medical records information. Totally, 173 cases were included in the study.

The cases were separated based on the TXA use. The clinical protocol allowed the administration of the highest TXA dose between 1 g or 10 mg/kg during anesthetic induction, with or without a dose replication just before the tourniquet deflation.

Demographic data were collected. In addition, information regarding the administered TXA dose, the levels of preoperative hemoglobin (Hb), the hemoglobin on the 3rd postoperative day, and the drain output on the 1st postoperative day were evaluated. The need for transfusion was indicated intraoperatively by the anesthesiologist according to subjective criteria, or by the clinician postoperatively, when Hb < 7 g/dl or Hb > 7 g/dl with clinical repercussions. Thromboembolic complications or hematoma formation requiring joint aspiration, and the total hospital/ICU length of stay were analyzed. As an exploratory analysis, this study also compared the patients' subgroup that received or not blood transfusion, regarding the need for hospitalization in the ICU, and the total hospital and ICU length of stay.

Statistical analysis

Numerical variables were described as mean and standard deviation when normal distribution in groups, or as median and interquartile range (IR) when non-normal distribution, according to Shapiro-Wilk test and Histogram analysis. Categorical variables were described by the absolute number and percentage within the group. In the univariate analyses, for numerical variables between groups, the Student's t-test or the Mann-Whitney U test was used, according to the variable's normality. In the categorical variables the Fisher's test in the respective contingency tables was used. To evaluate the determinants of the need for transfusion with control of possible confounding variables, multivariate binomial logistic regression was performed, including the following variables: sex, age, use of tranexamic acid, and drain use. Statistical significance was considered when $p < 0.05$.

RESULTS

Demographic characteristics

From 2013 to 2017, a total of 220 patients undergoing primary TKA surgery in our service had their data adequately recorded. Of this total, 173 patients were included based on the eligibility criteria of this study. Demographic characteristics showed no significant difference between groups (Table 1). Forty-seven (57.3%) patients received two doses of TXA.

Table 1. Patient demographics. Age is shown in years ± *standard deviation*; sex and diagnosis are described as *n* (%).

	TXA Group (n = 82)	Control group (n = 91)	TOTAL (n = 173)	*p**
Age	66.5 11.4	65.4 10.4	65.9 10.9	0.525
Sex				0.318
Male	18 (22)	26 (28.6)	44 (25.4)	
Female	64 (78)	65 (71.4)	129 (74.6)	
Diagnosis				0.864
Primary Osteoarthritis	64 (78)	72 (79.1)	136 (78.6)	
Others	18 (22)	19 (20.9)	37 (21.4)	

**Fisher's Test*

Blood loss

Table 2 shows the parameters associated to blood loss, such as Hb levels, drain output, and need for transfusion.

Table 2. Values related to blood loss. The values are shown as mean ± *standard deviation* or as median/IR. In the case of blood transfusion, the values are expressed in n (%).

	TXA group	Control group	*p*
Hb preoperative	13.57 1.32	13.54 1.26	0.867[1]
Hb postoperative (PO)	10.87 1.66	10.13 1.42	**0.002**[1]
Hb decrease	2.70 1.39	3.41 1.34	**< 0.001**[1]
1st PO drain output	270/290	460/575	**< 0.001**[2]
Blood transfusion	3 (10)	27 (90)	**< 0.001**[1]

1: Student's t-test; 2: Mann-Whitney U test.

The mean preoperative Hb was 13.5 g/dl (± 1.32) in the TXA group and 13.5 g/dl (± 1.26) in the control group ($p = 0.867$). On the 3rd postoperative day, the Hb levels were significantly higher in the TXA group in comparison with the control group (10.87 g/dl ± 1.66 vs 10.13 g/dl ± 1.42, respectively). TXA-treated patients had a smaller Hb decrease than the control group (2.7 g/dl ± 1.39 vs 3.41 g/dl ± 1.34; $p < 0.001$). Moreover, the median drain output on the 1st postoperative day was significantly reduced in the TXA group when compared with the control group.

Hemotransfusion was performed in 30 patients. Most transfusion cases were from the control group (90%), while a small proportion of the TXA-treated patients (10%) needed transfusion.

Length of stays and need for ICU

The mean length of stay in hospital was 5.17 days for the TXA group and 7.70 for the control one. Regarding the need for ICU,

62 (35.8%) patients required intensive postoperative support, 28 (34.1%) in the TXA group and 34 (37.4%) in the control group. The mean ICU length stay was 0.41 (± 0.68) days for the TXA group and 1.86 (± 7.66) for the control group.

As an exploratory analysis, this study correlated blood transfusion with the total hospital and ICU length of stay. For patients undergoing transfusion, the mean total hospitalization stay was 13.83 days, compared with 4.97 days of non-transfused patients ($p = 0.002$). Similarly, the mean ICU stay was 5.17 days for those who received blood and 0.34 days for those who did not receive blood transfusion ($p < 0.001$).

Moreover, the relationship between transfusion events and the need for ICU admission also showed statistical significance. Of the 30 patients receiving transfusion, 19 (63.3%) were referred to the ICU, while 11 (36.7%) did not require intensive care ($p = 0.001$).

Complications

Thromboembolic events and hematoma formation were evaluated as complications of TKA and accounted for 8.67% of the participants. Thromboembolic events occurred in 5 cases and hematoma formation that required joint aspiration occurred in 10 cases. No statistically significant difference was found between the groups (Table 3).

Table 3. Complications. The values are shown in n (%).

	TXA group	Control group	TOTAL	p*
Thromboembolic events	2 (2.4)	3 (3.3)	5 (2.9)	> 0.999
Hematoma	4 (4.9)	6 (6.6)	10 (5.8)	0.750

*Fisher's Test.

The multivariate evaluation by logistic regression was performed and included the following variables: sex, age, use of tranexamic acid, and drain output. Among the variables, only the use of TXA was correlated to the need for blood transfusion (odds ratio [OR], 0.097 {95% confidence interval [CI]}; 0.027-0.344, $p = 0.001$). This suggests the TXA afforded a protection from the need for transfusion of approximately 10 times.

DISCUSSION

In this study, we showed the effective use of TXA in decreasing the perioperative transfusion requirement. In addition, it reduced the hemoglobin decrease and the drain output on the 1st postoperative day. These results are similar to those found in the literature. Many studies show a favorable correlation between the use of TXA and the decrease in intra and postoperative bleeding during the TKA surgery.[10,11] Its efficacy and safety has been well studied recently.[12] A Cochrane review conducted by Henry et al. (2011) showed that TXA efficiently decreased blood loss during and after orthopedic procedures, reducing it in approximately 446.19 ml (95%CI 554.61-337.78 ml).[13] In this regard, Yang et al.[7], in a meta-analysis study, showed a significantly lower value in blood transfusion rates in patients who used TXA compared with the placebo group (OR 0.16, 95%CI 0.10-0.25; $p < 0.001$) (7). Similarly, the systematic review and meta-analysis conducted by Alshryda et al. (2011) show the use of TXA significantly reduced perioperative blood loss in over 591 ml (95%CI 536-647; $p < 0.001$) and the need for blood transfusion (RR 2.56, 95% CI 2.1-3.1; $p < 0.001$), without increasing the risk of adverse events, regardless of the via of administration (oral, topical, or intravenous).[14]

Besides the growing interest in TXA studies, there is no absolute conclusion of the best administration *via* (intravenous, intra-articular, topical, or oral)[15], dose, and the number of required applications for the best results.[8] The review performed by Melvin et al.[16] indicates that the effective dose has ranged from 1 g to 10-20 mg/kg of TXA, applied intravenously or topical, without significant different outcome. Although it is proposed that the number of doses may influence the reduction of blood loss[17], there is no consensus about the best administration regimen. In this study, the TXA was administered intravenously using the highest dose between 1 g or 10 mg/kg during anesthetic induction. Some of the cases had the treatment replicated immediately before the pneumatic tourniquet disinflation. Given the retrospective analysis of this study, there was no dose standardization, which is a limitation of the study.

Despite the good obtained results, the TXA also presents theoretical risks, such as deep vein thrombosis (DVT) and pulmonary thromboembolism (PE). Based on its mechanism of action, TXA might activate coagulation cascade and increase the tendency of thrombus formation. However, Alshryda et al.[14] showed no increase in the risk of these complications after the use of the TXA. Moreover, Sabbag et al.[18] conducted a retrospective study of patients with thromboembolic events history prior to TKA. They concluded that the recurrence of these events is uncommon after surgery, with no significant increase in incidence related to the use of TXA compared with the placebo group (2.3% versus 1.9% respectively; $p = 0599$).[18]

The incidence of DVT and pulmonary embolism after TKA surgery without an adequate prophylaxis was estimated to be 41%-85% and 1.5%-10%, respectively. Adequate prophylaxis reduces this incidence to approximately 1% during hospitalization.[19] In this study, prophylaxis was made with Enoxaparin 40 mg/day for 14 days. The study found 5 thromboembolism events, 2 (2.4%) of those in TXA group and 3 (3.3%) in the control group, without significant association regarding the use of TXA ($p > 0999$). The perioperative blood transfusion itself could also increase the risk of DVT after arthroplasty surgeries, by increasing blood viscosity, causing erythrocytes and platelets aggregation with subsequent thrombus formation.[20] Thus, decreasing the number of blood transfusions would improve the occurrence of these events.

As stated in this study with exploratory analysis, patients undergoing blood transfusion have a greater need for postoperative intensive care. Likewise, there was a positive correlation between the blood transfusion and the hospital and ICU length of stay. The use of TXA, by reducing the need for blood transfusion, would also be beneficial in decreasing the need for postoperative ICU, and the hospital and ICU length of stay. Randomized controlled trials are required to improve the understanding of this correlation.

The study had several limitations. Because it is a retrospective study, the patients may have different demographic characteristics. Moreover, as mentioned before, there was no standardization in the number of TXA applications (one or two doses). It was not possible to define the dose influence that in fact decreases perioperative bleeding. Additional studies would be useful to clarify these variables. Another limitation is the lack of real blood loss measurement, which was made by indirect methods, such as drain output and Hb decrease. Of note, there is a small difference in postoperative Hb between the groups, despite the statistically significant result (averages of 2.7 g/dl (± 1.39) in the TXA group and 3.41 g/dl (± 1.34) in the control group. This value refers to the 3rd postoperative day and, therefore, after blood transfusions. Since the control group was subjected to a more expressive number of transfusions, the Hb could be underestimated in these cases.

In this study, the primary outcome was the reduction of blood transfusions required after the TKA. The study considered this as one of the most faithful clinical expressions of blood loss. It is important

to emphasize that the indication for postoperative transfusion was made by a clinical team, which was unaware of the TXA use. Despite the limitations, this study is one of the few in the national literature to compare the use of TXA with a control group. Furthermore, the study shows the successful use of TXA in reducing the transfusion requirement, the postoperative Hb decrease, and the drain output in a pragmatic situation of an uncontrolled study.

CONCLUSION

In conclusion, the use of TXA had a positive role after TKA in our service. It significantly reduced the blood transfusion rates, being a potent tool in the therapeutic arsenal, aiming to improve the clinical and surgical conditions related to the TKA procedure and the perioperative period.

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REFERENCES

1. Levine BR, Haughom B, Strong B, Hellman M, Frank RM. Blood management strategies for total knee arthroplasty. J Am Acad Orthop Surg. 2014;22(6):361-71.
2. Wong J, Abrishami A, El Beheiry H, Mahomed NN, Roderick Davey J, Gandhi R, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am. 2010;92(15):2503-13.
3. Tang Y, Wen Y, Li W, Li H, Yang Y, Liu Y. The efficacy and safety of multiple doses of oral tranexamic acid on blood loss, inflammatory and fibrinolysis response following total knee arthroplasty: a randomized controlled trial. Int J Surg. 2019;65:45-51.
4. Huang Z, Huang C, Xie J, Ma J, Cao G, Huang Q, et al. Analysis of a large dataset to identify predictors of blood transfusion in primary total hip and knee arthroplasty. Transfusion. 2018;58(8):1855-62.
5. Su EP, Su S. Strategies for reducing peri-operative blood loss in total knee arthroplasty. Bone Joint J. 2016;98-B(1):98-100.
6. Riaz O, Aqil A, Asmar S, Vanker R, Hahnel J, Brew C, et al. Epsilon-aminocaproic acid versus tranexamic acid in total knee arthroplasty: a meta-analysis study. J Orthop Traumatol. 2019;20(1):28.
7. Yang ZG, Chen WP, Wu LD. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. J Bone Joint Surg Am. 2012;94(13):1153-9.
8. Kim TK, Chang CB, Koh IJ. Practical issues for the use of tranexamic acid in total knee arthroplasty: a systematic review. Knee Surg Sports Traumatol Arthrosc. 2014;22(8):1849-58.
9. Pabinger I, Fries D, Schöchl H, Streif W, Toller W. Tranexamic acid for treatment and prophylaxis of bleeding and hyperfibrinolysis. Wien Klin Wochenschr. 2017;129(9-10):303-16.
10. Tanaka N, Sakahashi H, Sato E, Hirose K, Ishima T, Ishii S. Timing of the administration of tranexamic acid for maximum reduction in blood loss in arthroplasty of the knee. J Bone Joint Surg Br. 2001;83(5):702-5.
11. Sassoon A, Nam D, Jackups R, Johnson SR, Nunley RM, Barrack RL. Tranexamic acid: optimal blood loss management in surface replacement arthroplasty. Bone Joint J. 2016;98-B(2):173-8.
12. Whiting DR, Gillette BP, Duncan C, Smith H, Pagnano MW, Sierra RJ. Preliminary results suggest tranexamic acid is safe and effective in arthroplasty patients with severe comorbidities. Clin Orthop Relat Res. 2014;472(1):66-72.
13. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, Ker K. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2011;(1):CD001886.
14. Alshryda S, Sarda P, Sukeik M, Nargol A, Blenkinsopp J, Mason JM. Tranexamic acid in total knee replacement: a systematic review and meta-analysis. J Bone Joint Surg Br. 2011;93(12):1577-85.
15. Xu S, Chen JY, Zheng Q, Lo NN, Chia SL, Tay KJD, et al. The safest and most efficacious route of tranexamic acid administration in total joint arthroplasty: a systematic review and network meta-analysis. Thromb Res. 2019;176:61-6.
16. Melvin JS, Stryker LS, Sierra RJ. Tranexamic acid in hip and knee arthroplasty. J Am Acad Orthop Surg. 2015;23(12):732-40.
17. Drosos GI, Ververidis A, Valkanis C, Tripsianis G, Stavroulakis E, Vogiatzaki T, Kazakos K. A randomized comparative study of topical versus intravenous tranexamic acid administration in enhanced recovery after surgery (ERAS) total knee replacement. J Orthop. 2016;13(3):127-31.
18. Sabbag OD, Abdel MP, Amundson AW, Larson DR, Pagnano MW. Tranexamic acid was safe in arthroplasty patients with a history of venous thromboembolism: a matched outcome study. J Arthroplasty. 2017;32(9S):S246-50.
19. Januel JM, Chen G, Ruffieux C, Quan H, Douketis JD, Crowther MA, et al. Symptomatic in-hospital deep vein thrombosis and pulmonary embolism following hip and knee arthroplasty among patients receiving recommended prophylaxis: a systematic review. JAMA. 2012;307(3):294-303.
20. Jiang T, Song K, Yao Y, Pan P, Jiang Q. Perioperative allogenic blood transfusion increases the incidence of postoperative deep vein thrombosis in total knee and hip arthroplasty. J Orthop Surg Res. 2019;14(1):235.