OBJECTIVE: To compare the use of intravenous and topical tranexamic acid (TXA) in unilateral primary total knee arthroplasty (TKA) in relation to blood loss and complications inherent to the medication. Method: Three groups with 14 patients each were constituted, and all of them were operated using the same surgical technique. In Group 1, usual measures for bleeding control were performed. Group 2 patients received TXA topically on the joint surface. In Group 3, intravenous TXA was used. Hemoglobin (HB), hematocrit (HTC), platelets (PLAT), prothrombin time, activated partial thromboplastin time and volume of blood drained observed 24 hours after arthroplasty were compared to the values of tests found before surgery. Results: There was a decrease in the concentration of HB, HTC and PLAT in all groups in relation to the preoperative, however without significant difference. Group 3 had a lower mean volume of drained blood than the other groups, with statistical significance. No adverse effects or thromboembolic events were observed in the groups that received TXA. Conclusion: This study showed superiority in the use of intravenous TXA in decreasing the volume of bleeding, without increasing the risk of thromboembolic events. Level of Evidence I, High quality randomized trial with statistically significant difference or no statistically significant difference but narrow confidence intervals.

Keywords: Tranexamic Acid. Arthroplasty. Knee. Hemorrhage. Antifibrinolytic Agents. Osteoarthritis. Knee.

INTRODUCTION

Osteoarthritis (OA) of the knee is one of the most common causes of disability and its prevalence is increasing as older and obese populations grow. More than 50% of people over the age of 65 have radiographic changes in the knee that indicate OA. The risk of developing OA in the knee is due to a multifactorial and complex interaction of constitutional and mechanical factors. Initial and conservative treatment can be non-pharmacological, including weight loss, aerobic exercise, osteopathic manipulative treatment, or pharmaceutical treatment. In refractory or advanced cases, total knee arthroplasty (TKA) is now a commonly performed surgical procedure. TKA allows the patient to move the knee without pain, in addition to maintaining a wide range of daily activities, permitting them to lead a normal life. However, it is associated with large amounts of

The study was conducted at Hospital da Santa Casa de Misericórdia de Vitória. Correspondence: Otávio Montovanelli Monteiro. Rua Desembargador Augusto Botelho, 645, apto. 304, Vila Velha, ES, Brazil, 29101110. otaviomm88@gmail.com

Article received on 03/28/2020, approved on 08/27/2020.
perioperative blood loss and high blood transfusion rates. The blood loss may come from the osteotomized surface of the distal femur and the proximal tibia, from the release of soft tissues and dredging of the marrow cavity. The use of chronic anticoagulant medication and the early rehabilitation of joint function also results in postoperative anemia, which are common concerns for postoperative complications after TKA surgery. This finding has led surgeons and researchers to seek pharmacological and mechanical means to avoid this perioperative blood loss as much as possible and to reduce transfusion rates. Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that inhibits fibrinolysis by competitively blocking plasminogen lysine binding sites. Studies have shown that administration of tranexamic acid decreases bleeding after a series of surgical procedures including TKA, without predisposing to thromboembolic complications. Thus, the present study compared two methods of administering TXA – topical intra-articular and intravenous – with each other and in relation to a control group, with the main objective of evaluating the effectiveness in reducing bleeding and the need for blood transfusion in patients submitted to unilateral primary TKA, in addition to observing the safe use of TXA (secondary objective).

METHOD

Study design, participation criteria and sample size

This is a prospective, randomized study, initiated after approval by the Human Research Ethics Committee of the Higher School of Sciences of Santa Casa de Misericórdia de Vitória, institution where the surgeries were performed, published on Plataforma Brasil with the number of opinion 2,449,068. All procedures are in accordance with the 1995 Helsinki declaration. Patients were invited to participate in the research after being duly informed. All signed the Informed Consent Form. The doctor who followed the evolution of patients after the surgical procedures did not participate in them, and was not informed about which line of treatment the patient had been submitted to, so that there was no influence of results at the time of data collection. The procedures were performed in the operating room of a philanthropic hospital in the city of Vitória, state of Espírito Santo, Brazil, which provided access to patient identification data and treatment lines, so that there could be data analysis at the end of the procedure study. The study included patients older than 55 years in advanced stage of primary knee osteoarthritis according to the criteria of the American College of Rheumatology and with grade IV radiological changes according to the Kellgren and Lawrence classification. Patients with acute occlusive vasculopathy, hypersensitivity to the components of the tranexamic acid formula, no indication for primary total knee arthroplasty, those who abuse alcohol and medications, and who use glucocorticoids or opioids daily were not included.

The total sample size was 42 patients (N = 42) divided equally in three groups (14 in each). The sample size was calculated for comparison among the three groups using the G-Power program, considering the sample size calculation for fixed event analysis, an effect size of 0.5, significance of 5%, power of the 80% test. In a previously prepared sealed container, 42 envelopes (14 from each group) were inserted, which were randomly selected by a team member on the day of surgery.

TABLE 1. Comparing preoperative and postoperative moments by group for hemoglobin.

| Group | Pre | Mean | Median | Standard Deviation | DC | Min | Max | N | CI | P-value |
|-------|-----|------|--------|--------------------|----|-----|-----|---|----|---------|
| Group 1 | 13.18 | 12.8 | 1.24 | 9% | 11.4 | 15.4 | 14 | 0.65 | <0.001* |
| Group 2 | 10.36 | 10.4 | 1.25 | 12% | 8.1 | 12.9 | 14 | 0.65 | <0.001* |
| Group 3 | 13.48 | 13.5 | 0.94 | 7% | 11.9 | 15.4 | 14 | 0.49 | <0.001* |

*HB, hemoglobin; Pre, preoperative; Post, postoperative; DC, derivation coefficient; Min, minimum; Max, maximum; N, sample size; CI, confidence interval

<0.001* Considered statistically significant

RESULTS

We observed that there is a mean difference between the pre and postoperative moments for the variables HB, HTC and PLAT in the three groups, (Tables 1, 2 and 3). We did not observe a statistically significant mean difference between the groups for the variation (delta) of HB, HTC and PLAT (Table 4).
Table 2. Comparing preoperative and postoperative moments by group for hematocrit.

|        | Mean  | Median | Standard Deviation | DC | Min  | Max  | N  | CI     | P-value |
|--------|-------|--------|--------------------|----|------|------|----|--------|---------|
| Group 1 | Pre   | 39.54  | 39.4               | 3.68 | 9%   | 34.4 | 45.8 | 1.93   | <0.001* |
|         | Post  | 30.54  | 30.7               | 3.35 | 11%  | 23.9 | 36.3 | 1.75   |         |
| Group 2 | Pre   | 40.44  | 40.3               | 2.81 | 7%   | 34.7 | 45.3 | 1.47   | <0.001* |
|         | Post  | 32.71  | 32.4               | 3.37 | 10%  | 27.3 | 38.4 | 1.77   |         |
| Group 3 | Pre   | 39.65  | 40.7               | 3.70 | 9%   | 33.0 | 44.7 | 1.94   | <0.001* |
|         | Post  | 30.81  | 30.8               | 4.84 | 16%  | 23.2 | 38.9 | 2.54   |         |

HTC, hematocrit; Pre, preoperative; Post, postoperative; DC, derivation coefficient; Min, minimum; Max, maximum; N, sample size; CI, confidence interval

Table 3. Comparing preoperative and postoperative moments by group for platelets.

|        | Mean  | Median | Standard Deviation | DC | Min  | Max  | N  | CI     | P-value |
|--------|-------|--------|--------------------|----|------|------|----|--------|---------|
| Group 1 | Pre   | 230.607| 233.000            | 51.136| 22%  | 129.000 | 309.000 | 14 | 26.786 | <0.001* |
|         | Post  | 171.500| 169.000            | 37.910| 22%  | 110.000 | 245.000 | 14 | 19.858 |         |
| Group 2 | Pre   | 214.286| 210.500            | 48.175| 22%  | 156.000 | 299.000 | 14 | 25.235 | 0.022   |
|         | Post  | 183.357| 178.000            | 31.532| 17%  | 137.000 | 236.000 | 14 | 16.517 |         |
| Group 3 | Pre   | 224.407| 233.000            | 38.426| 17%  | 139.000 | 292.000 | 14 | 20.128 | <0.001* |
|         | Post  | 173.071| 180.000            | 28.261| 16%  | 126.000 | 219.000 | 14 | 14.804 |         |

PLAT, platelets; Pre, preoperative; Post, postoperative; DC, derivation coefficient; Min, minimum; Max, maximum; N, sample size; CI, confidence interval

*Considered statistically significant

Table 4. Comparison of the observed variation of HB, HTC and PLAT between the Groups.

|        | Mean  | Median | Standard Deviation | DC | Min  | Max  | N  | CI     | P--value |
|--------|-------|--------|--------------------|----|------|------|----|--------|----------|
| HB     | Group 1 | -2.82  | -2.66              | 1.11 | 39%  | -4.50 | 1.00 | 14 | 0.58    | 0.756    |
|        | Group 2 | -2.49  | -2.25              | 1.16 | 47%  | -4.70 | -1.10 | 14 | 0.61    |         |
|        | Group 3 | -2.66  | -2.55              | 1.19 | 44%  | -5.30 | -1.00 | 14 | 0.62    |         |
| HTC    | Group 1 | -8.99  | -8.90              | 3.71 | 41%  | -16.10| -2.80 | 14 | 1.94    | 0.570    |
|        | Group 2 | -7.73  | -6.50              | 3.28 | 42%  | -13.40| -4.10 | 14 | 1.72    |         |
|        | Group 3 | -8.84  | -8.40              | 3.26 | 37%  | -14.50| -2.70 | 14 | 1.71    |         |
| PLAT   | Group 1 | -59.107| -60.500            | 29.031| 49%  | -122.500| -17.000 | 14 | 15.207 | 0.104    |
|        | Group 2 | -30.929| -17.000            | 45.171| 144% | -138.000| 8.000 | 14 | 23.319 |         |
|        | Group 3 | -51.336| -58.500            | 29.693| 58%  | -91.000| 23.000 | 14 | 15.554 |         |

HB, hemoglobin; HTC, hematocrit; PLAT, platelets; Pre, preoperative; Post, postoperative; DC, derivation coefficient; Min, minimum; Max, maximum; N, sample size; CI, confidence interval

The comparison of the volume of blood drained (Graph 1) showed a statistical difference between the groups (Table 5). We observed that this difference was made between Group 1 compared to Group 3 (Table 6).
In addition to elective surgery, TXA is also used successfully, gaining adherents and being the target of several studies. Among its early (before skin suture) or late (after dressing the compressive dressing) applications that still need a definitive resolution, including intra and postoperative bleeding with consequent hemodynamic complications and infectious disorders. Tranexamic acid proved to be safe, once no possible adverse reactions from its use or thromboembolic events were observed in patients in the groups in which it was administered. One patient in the control group had pulmonary thromboembolism. Only one patient in group 3 required blood transfusion in the postoperative period. There were no surgical complications, death or other complications during the experiment.

**DISCUSSION**

TKA is recognized as a successful procedure, increasingly performed in orthopedics, since the population has aged and needs a better quality of life. However, TKA has some complications that still need a definitive resolution, including intra and postoperative bleeding with consequent hemodynamic and infectious disorders.

The use of a tourniquet is capable of considerably diminishing intraoperative bleeding, contributing to decrease hemodynamic effects as well as allowing for cleaner surgery, even facilitating the cementation of implants. However, when it is used, most bleeding in TKA occurs after its release, with no significant difference between its early (before skin suture) or late (after dressing the compressive dressing). Therefore, the use of pharmacological strategies aimed at reducing bleeding, especially after the release of ischemia, has been both gaining adherents and being the target of several studies. Among these strategies, the use of TXA draws attention. In addition to elective surgery, TXA is also used successfully, reducing the need for transfusions and death from hypovolemic shock in trauma victims, without increasing the risk of thromboembolic events.

The way in which TXA has been administered varies, however. The present study sought to compare two different strategies for using TXA: topical intra-articular application and intravenous use. Our results demonstrated that both topical and intravenous use of TXA is safe, since no adverse effects or increased thromboembolic events were observed when compared with the control group. Besides, these results are in line with other studies who used TXA in knee arthroplasties in different doses and forms of application. The study by Aggarwal et al. observed a lower volume of bleeding when topical rather than intravenous TXA was used in bilateral primary knee arthroplasties performed simultaneously. In our comparison, we evidenced that the intravenous use of TXA was more effective in reducing bleeding in the postoperative period than topical application, with a significant result. The volume of blood drained in 24 hours was, on average, 341.1 ml for group 2 and 180.1 ml for group 3. However, there was no statistically significant decrease in the loss of hemoglobin and hematocrit between the groups. A similar result was also observed in a study alike ours, even though the doses of TXA administered varied. Even so, taking into account the possible complications of hematoma formation, such as infections, delayed healing and increased postoperative pain, we can infer the advantage of intravenous use of TXA.

**CONCLUSION**

Our study showed superiority in the use of intravenous tranexamic acid in relation to the topical use of tranexamic acid and the control group, in view of the lower volume of blood drained. The use of tranexamic acid proved to be safe, once no possible adverse reactions from its use or thromboembolic events were observed in patients in the groups in which it was administered.

**AUTHORS’ CONTRIBUTIONS:** Each author contributed individually and significantly to the development of this article. OMM: substantial contribution to the work in its conception and design, data collection, analysis and interpretation, writing and critical review of its intellectual content; RTP: substantial contribution to the work in its conception and design, data collection, analysis and interpretation, writing and critical review of its intellectual content; FNA: data analysis and interpretation, writing and critical review of its intellectual content; CPM: data collection, analysis and interpretation, writing and critical review of its intellectual content; SGO: data collection, analysis and interpretation, and critical review of its intellectual content; GDBA: substantial contribution to the work in its conception and design, data collection, analysis and interpretation, writing and critical review of its intellectual content.
REFERENCES

1. Arden N, Nevitt MC. Osteoarthritis: epidemiology. Best Pract Res Clin Rheumatol. 2006;20(1):3-25.

2. Aggarwal AK, Singh N, Sudeep P. Topical vs Intravenous Tranexamic Acid in Reducing Blood Loss After Bilateral Total Knee Arthroplasty: A Prospective Study. J Arthroplasty. 2016;31(7):1442-8.

3. Kim RH, Springber BD, Douglas DA. Knee reconstruction and replacement. In: Flynn F, editor. Orthopaedic knowledge update. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2011. p. 469-75.

4. Sehat KR, Evans RL, Newman JH. Hidden blood loss following hip and knee arthroplasty. Correct management of blood loss should take hidden loss into account. J Bone Joint Surg Br. 2004;86(4):561-5.

5. Good L, Peterson E, Lisander B. Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement. Brit J Anaesth. 2003;90(5):596-9.

6. Henry DA, Carless PA, Moxey AJ, O’Connell D, Stokes BJ, Ferguson DA, Ker K. Antifibrinolytic use for minimizing perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2011;(1):CD001886.

7. Coetzee MJ. The use of topical crushed tranexamic acid tablets to control bleeding after dental surgery and from skin ulcers in haemophilia. Haemophilia. 2007;13(4):443-4.

8. Wong J, Abrishami A, El Beheiry H, Mahomed NN, Davey JR, 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.

9. CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomized, placebo-controlled trial. Lancet. 2010;376(9734):23-32.

10. Jixiang T, Hong C, Qin L, Cheng C, Wei H. A meta-analysis of the effectiveness and safety of using tranexamic acid in primary unilateral total knee arthroplasty. J Surg Res. 2013;184(2):880-7.

11. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of knee. Arthritis Rheum. 1986;29(6):1039-49.

12. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthritis. Ann Rheum Dis. 1957;16(4):494-502.

13. Bidolegui F, Arce G, Lugones A, Pereira S, Vindver G. Tranexamic Acid Reduces Blood Loss and Transfusion in Patients Undergoing Total Knee Arthroplasty without Tourniquet: A Prospective Randomized Controlled Trial. Open Orthop J. 2014;8:250-54.

14. Lima ALMM, Pécora JR, Albuquerque RM, Paula AP, D’Elia CO, Santos ALG, Croci AT. Infeção pós-artroplastia total do joelho: considerações e protocolo de tratamento. Acta Ortop Bras. 2004;12(4):236-41.

15. Ejaz A, Laursen AC, Kappel A, Laursen MB, Jakobsen T, Rasmussen S, Nielsen PT. Faster recovery without the use of a tourniquet in total knee arthroplasty. Acta Orthop. 2014;85(4):422-6.

16. Tsumura N, Yoshiya S, Chin T, Shibata R, Kohso K, Doita M. A prospective comparison of clamping the drain or post-operative salvage of blood in reducing blood loss after total knee arthroplasty. J Bone Joint Surg Br. 2006;88(1):49-53.

17. Leão MGS, Souza HAP, Ferreira YMC. Avaliação da perda sanguínea após a liberação precoce ou tardia da isquemia em pacientes submetidos à artroplastia total do joelho. Rev Bras Ortop. 2013;48(2):152-8.

18. Zekcer A, Del Priori R, Tieppo C, Silva RS, Severino NR. Estudo comparativo com uso do ácido tranexâmico tópico e intravenoso em relação à perda sanguínea na artroplastia total do joelho. Rev Bras Ortop. 2017;52(5):589-95.

19. Andrade MAP, Campos TVO, Silva BFA, Assis ME, Boechat LC, Bioni LF, et al. Avaliação prospectiva dos pacientes submetidos à artroplastia total do joelho com e sem colocação de dreno de sucção. Rev Bras Ortop. 2010;45(6):549-53.

20. Esler CNA, Blakeway C, Fiddian NJ. The use of a closed-suction drain in total knee arthroplasty. A prospective randomised study. J Bone Joint Surg Br. 2003;85(2):215-7.