Research, Society and Development, v. 11, n. 15, e160111537094, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i15.37094

Thromboembolic event index after total knee arthroplasty with the use of tranexamic acid: an integrative review

Índice de eventos tromboembólicos após artroplastia total do joelho com uso de ácido tranexâmico: uma revisão integrativa

Tasa de eventos tromboembólicos después de la artroplastia total de rodilla con ácido tranexámico: una revisión integradora

Received: 10/26/2022 | Revised: 11/03/2022 | Accepted: 11/06/2022 | Published: 11/13/2022

Rafael Rosano Gotti Alves
ORCID: https://orcid.org/0000-0002-8293-6587
University of Uberaba, Brazil
E-mail: gotti.joelho@gmail.com
José Martins Juliano Eustáquio
ORCID: https://orcid.org/0000-0002-6230-0258
University of Uberaba, Brazil
E-mail: zemartinsjuliano@hotmail.com
Sandro Marcílio Pereira Gomes
ORCID: https://orcid.org/0000-0002-9181-7707
Federal University of Triângulo Mineiro, Brazil
E-mail: smpgomes@hotmail.com
Maria Laura Oliveira Morais
ORCID: https://orcid.org/0000-0002-3919-6114
University of Uberaba, Brazil
E-mail: marialauramorais_@hotmail.com
João Cesar Oliveira Morais
ORCID: https://orcid.org/0000-0002-4577-4494
Faculty Ceres, Brazil
E-mail: joaocesarmorais@hotmail.com
Amanda Viera Sacardo
ORCID: https://orcid.org/0000-0002-3297-4753
University of Uberaba, Brazil
E-mail: amandavsacardo@gmail.com
Eduardo Rodrigues Parreira
ORCID: https://orcid.org/0000-0002-1796-8865
University of Uberaba, Brazil
E-mail: eduparreira@gmail.com

Abstract
Total knee arthroplasty (TKA) is a surgical procedure that consists of replacing the weight-bearing surfaces of the affected joint with a prosthesis, aiming at relieving pain and correcting deformities. Due to the inherent risk of venous thromboembolism, drugs are used for its prophylaxis. This integrative literature review aimed to analyze the complications involved in the use of tranexamic acid in patients undergoing total knee arthroplasty (TKA), specifically the thromboembolic events that occurred. Studies were selected from PubMed, SciELO, Medline and Thieme electronic databases. Eleven randomized clinical trials were included. The total number of patients included in the studies was 1.299 who underwent TKA. In total, seven thromboembolic events were recorded, thus occurring in 0.5% of the cases analyzed. Thus, the safety of the use of tranexamic acid is proven, so that 99.5% of the patients did not present thromboembolic events, with the index relative to positive cases being practically irrelevant. Thus, the concluion is that the drug is safe and effective to be used in this surgical procedure, in order to minimize bleeding, rarely resulting in thromboembolic events.
Keywords: Knee; Arthroplasty; Thromboembolism; Tranexamic acid.

Resumo
A artroplastia total do joelho (ATJ) é um procedimento cirúrgico que consiste na substituição das superfícies de sustentação de peso da articulação afetada por uma prótese, com o objetivo de aliviar a dor e corrigir deformidades. Devido ao risco inerente de tromboembolismo venoso, drogas são utilizadas para sua profilaxia. Esta revisão integrativa da literatura teve como objetivo analisar as complicações envolvidas no uso do ácido tranexâmico em pacientes submetidos à artroplastia total do joelho (ATJ), especificamente os eventos tromboembólicos ocorridos. Os estudos

foram selecionados nas bases de dados eletrônicas PubMed, SciELO, Medline e Thieme. Onze ensaios clínicos randomizados foram incluídos. O número total de pacientes incluídos nos estudos foi de 1.299 submetidos à ATJ. No total, foram registrados sete eventos tromboembólicos, ocorrendo assim em 0,5% dos casos analisados. Assim, fica comprovada a segurança do uso do ácido tranexâmico, de modo que 99,5% dos pacientes não apresentaram eventos tromboembólicos, sendo praticamente irrelevante o índice relativo aos casos positivos. Assim, conclui-se que o fármaco é seguro e eficaz para ser utilizado neste procedimento cirúrgico, a fim de minimizar o sangramento, raramente resultando em eventos tromboembólicos.
Palavras-chave: Joelho; Artroplastia; Tromboembolismo; Ácido tranexâmico.

Resumen
La artroplastia total de rodilla (ATR) es un procedimiento quirúrgico que consiste en sustituir las superficies de carga de la articulación afectada por una prótesis, con el objetivo de aliviar el dolor y corregir las deformidades. Debido al riesgo inherente de tromboembolismo venoso, se utilizan fármacos para su profilaxis. Esta revisión integradora de la literatura tuvo como objetivo analizar las complicaciones involucradas en el uso de ácido tranexámico en pacientes sometidos a artroplastia total de rodilla (ATR), específicamente los eventos tromboembólicos ocurridos. Los estudios se seleccionaron de las bases de datos electrónicas PubMed, SciELO, Medline y Thieme. Se incluyeron once ensayos controlados aleatorios. El número total de pacientes incluidos en los estudios fue de 1.299 que se sometieron a ATR. En total se registraron siete eventos tromboembólicos, ocurriendo así en el 0,5% de los casos analizados. Así, queda demostrada la seguridad del uso del ácido tranexámico, de forma que el 99,5% de los pacientes no presentaron eventos tromboembólicos, siendo prácticamente irrelevante el índice relativo a los casos positivos. Por lo tanto, se concluye que el fármaco es seguro y eficaz para ser utilizado en este procedimiento quirúrgico, con el fin de minimizar el sangrado, resultando raramente en eventos tromboembólicos.
Palabras clave: Rodilla; Artroplastia; Tromboembolismo; Ácido tranexámico.

1. Introduction

Total knee arthroplasty (TKA) is a surgical procedure that consists of replacing the weight-bearing surfaces of the publication with a prosthesis, in order to relieve pain and disability and change deformities. Due to bone cutting, soft tissue manipulation and bone marrow violation, an average postoperative drop in hemoglobin of approximately 3g/dL and an estimated 300 to 1000mL of blood recovered postoperatively in drainage devices can be predicted (Padala *et al*., 2010; Roy *et al*., 2006).

Although the benefits of TKA are reduced from pain and improved function, there are also risks such as hemorrhage, thromboembolic events and infection (Tille *et al*., 2019). The control of massive bleeding that occurs during total arthroplasty has always been a difficult issue for surgeons, because blood loss can reduce antithrombin III levels and inhibit the endogenous fibrinolytic system, allowing the formation and thrombus growth at all levels (Bredbacka *et al*., 1987; Eriksson *et al*., 1989; Francis *et al*., 1988).

Tranexamic acid is an antifibrinolytic drug whose mechanism of action is through competitive inhibition of the activation of plasminogen into plasmin, the main agent responsible for fibrinolysis, through the adhesion of the acid to the binding sites of lysine in the plasminogen molecule, preventing that it binds to plasminogen activating factor (Boström *et al*., 2013). As it is a synthetic fibrinolysis inhibitor, recent studies are proposing the use in knee arthroplasty. Considering this scenario, strategies for the use of tranexamic acid aim to reduce the need for blood transfusion (Jeter *et al*., 1995).

However, there are still few studies regarding the complications of the use of this drug. There are some indices about the occurrence of deep vein thrombosis (DVT), a complex and silent disease that can bring serious complications when not treated quickly and properly. It consists of the formation of clots (thrombus) within a venous blood vessel with a consequent inflammatory reaction of the vessel, which may result in total or partial venous obstruction, leading to the interruption of blood flow (Albuquerque *et al*., 1997). The complication of this disease is pulmonary embolism (PE), in which one or more pulmonary arteries are blocked by a blood clot, most often originating in the lower limbs, episodes that can occur after the administration of tranexamic acid.

This study aimed to carry out a systematic review on the complications of the use of tranexamic acid in TKA surgeries, more specifically, the DVT and PTE index after the use of the drug.

2. Methodology

This study is an integrative review that is considered as a unique research on the health area, allowing an identification, synthesis and carrying out a broad analysis in the literature on a specific theme (Silva *et al*., 2020). Therefore, the following steps were used: delimitation of the guiding theme of the research, survey of publications based on literature analysis, classification and analysis of the information found, criticism of the included studies, discussion of the results and analysis of the findings and synthesis of the criticism (Souza *et al*., 2010).

This article was prepared from a review of the literature in the electronic databases PubMed, Scielo, Lilacs and Medline, from 1999 to 2020. The keywords used were "tranexamic acid", "knee", "arthroplasty" and "thromboembolic events". Inclusion criteria were articles referring to randomized clinical trials and prospective cohort studies, and the data analyzed referred to patients of any sex or age. Exclusion criteria were articles published before 1999, those that referred only to the benefits of the drug, those that compared tranexamic acid with another drug, and articles in which patients did not receive prophylactic anticoagulation.

Adding up all the databases, 597 articles were found. After reading the titles, it was noted that 264 were repeated in the different bases and another 237 did not meet the criteria of this study. A total of 96 articles were selected for reading the abstract, excluding those that did not fit the purpose of this study, being limited only to the benefits of tranexamic acid. After reading the abstracts, 22 articles were selected that met the initially proposed criteria and were read in full.

3. Results

In the final selection, only studies referring to randomized clinical trials were selected, resulting in 11 articles for the study, as described in Table 1.

Table 1 - Selection of articles in the databases.

Identification	Author	Year	Kind of study
1	Jansen e*t al.*	1999	Randomized clinical trial
2	Orpen *et al.*	2006	Randomized clinical trial
3	Volquind *et al.*	2014	Randomized clinical trial
4	Zekcer *et al.*	2016	Randomized clinical trial
5	Spanyer *et al.*	2016	Randomized clinical trial
6	Santias *et al.*	2017	Randomized clinical trial
7	Lee *et al.*	2017	Randomized clinical trial
8	Huang *et al.*	2017	Randomized clinical trial
9	Wang *et al.*	2018	Randomized clinical trial
10	Zhang *et al.*	2019	Randomized clinical trial
11	Tille *et al.*	2019	Randomized clinical trial

Source: Authors.

They are present in the following journals: Clinical Orthopedics and Related Research, The Medicine, Brazilian Vascular Journal, Journal of Bone and Joint Surgery, Journal of Knee Surgery, Brazilian Journal of Anesthesiology, European Journal of Orthopedic Surgery and Traumatology, Journal of Thrombosis and Haemostasis and British Journal of Anaesthesia. The main countries that developed the research were Brazil, the United States and China.

In the results that refer to the population studied, the individuals who participated in the initial evaluation and those who

were effectively evaluated were taken as a basis, according to the proposed criteria.

For the analysis of thromboembolic results, in the articles that included a control group and a group treated with tranexamic acid, only the events that occurred in the treatment group were considered, such as the number of participants and the DVT and PE rates.

The total number of patients included in the 11 studies was 1.660 who underwent TKA, of which 1.135 were female (68%) and 525 were male (32%). Of these patients, 467 received placebo and 1.193 received tranexamic acid. In the placebo group, seven DVT and no PE were recorded (1.5%); in the treatment group, there were five DVT and one PE (0.5%). The characteristics of the included studies are detailed in Table 2.

Table 2 - Specification of selected articles.

Identification	Placebo group	Acid treatment group
1	N=21: 18F e 3M DVT: 0 / PE: 0	N=21: 16F E 5M DVT: 0 / PE: 0
2	N=14: 11F e 3M DVT: 0 / PE: 0	N=15: 15F e 8M DVT: 0 / PE: 0
3	N=30: 21F e 9M DVT: 0 / PE: 0	N=32: 22F e 10M DVT: 0 / PE: 0
4	N=26: 25F e 1M DVT: 4 / PE: 0	N=59: 14F e 45M DVT: 1 / PE: 0
5	No placebo group	N=104: 66F e 38M DVT: 0 / PE: 0
6	N=115: 35F e 80M DVT: 0 / PE: 0	N=115: 74F e 41M DVT: 0 / PE: 0
7	No placebo group	N=376: 346F e 30M DVT: 0 / PE: 1
8	N=50: 35F e 15M DVT: 0 / PE: 0	N=100: 34F e 66M DVT: 0 / PE: 0
9	N=55: 36F e 19M DVT: 0 / PE: 0	N=220: 142F e 78M DVT: 0 / PE: 0
10	N=55: 43F e 12M DVT: 0 / PE: 0	N=50: 39F e 11M DVT: 0 / PE: 0
11	N=101: 65F e 36M DVT: 3 / PE: 0	N=101: 56F e 45M DVT: 4 / PE: 0

N= number of participants, F= female, M= male. Source: Authors.

Positive results for thromboembolic events

Zekcer *et al*. (2016) recorded one case of DVT, which was observed in the topical group (in the gastrocnemius vein), no cases in the intravenous group, and four cases in the placebo group (one in the popliteal vein and three in the gastrocnemius vein). All these events were diagnosed by duplex ultrasound and the patients were all asymptomatic. These five patients were medically treated by a vascular surgery specialist. The 30 patients in the "topical group" received a 1.5g solution of tranexamic

acid (50mg/ml, Transamin®) diluted in 50ml of 0.9% saline solution, which was sprayed for 5 minutes before releasing the tourniquet. The 30 patients in the "intravenous group" received 20mg/kg of medication, diluted in 100ml of 0.9% saline solution, for a period of ten minutes, at the same time as the anesthesia administration. All patients received prevention of venous thrombosis with elastic stockings and 40mg of enoxaparin sodium (Clexane®), administered subcutaneously, once daily, for ten days.

Lee *et al*. (2017) registered only one patient in the intravenous-only group with symptomatic pulmonary embolism, treated with low-molecular-weight heparin and warfarin without residual sequelae. Patients of the intravenous (IV) only group received intraoperatively weight-adjusted tranexamic acid (10 mg/kg) mixed in 100 mL of normal saline, 30 minutes before tourniquet deflation; the same dose was repeated three hours after surgery. For patients assigned to the intra-articular only (IA) group, 2.0 g of tranexamic acid in 30 mL of normal saline was injected into the joint after closure of the retinaculum and quadriceps tendon. Patients in the low-dose combination group received an IA injection of 1.0 g of tranexamic acid in 30 mL of normal saline, in addition to weight-adjusted IV and postoperative administrations. Similarly, patients in the high-dose combination group received an IA injection of 2.0 g of tranexamic acid in 30 mL of normal saline, in addition to intraoperative and postoperative intravenous administration of tranexamic acid. All patients received thromboprophylaxis according to the individualized approach protocol and were assessed preoperatively for risk of pulmonary embolism or bleeding and classified into four risk-stratified categories.

Tille *et al*. (2019) recorded one proximal and three distal deep vein thrombosis within the treatment group. Within the control group, three distal deep venous thromboses were observed. Patients received 2.0g (20 ml) of intra-articular tranexamic acid using a standard syringe after closing the joint capsule. Postoperatively, they received an antithrombotic drug after a standardized protocol. The medication consisted of rivaroxaban 10mg once daily, a direct Anti-Xa antagonist (Xarelto®) started six to eight hours after the surgical procedure. Patients with pre-existing anticoagulation received as suggested by the angiologist, usually low-molecular-weight heparin twice daily, using half the therapeutic dose omitting the immediate preoperative dose.

Negative results for thromboembolic events

Jansen *et al*. (1999) administered 15mg/kg of tranexamic acid to all patients 30min before tourniquet opening and surgery, subsequently repeated every eight hours for three days. Routinely, all patients were treated with low-molecular-weight heparin (Fraxiparin®) from the day before surgery until hospital discharge. To prevent intraoperative blood loss, a pneumatic tourniquet was inflated after the leg had been elevated for five minutes and was released at the end of the surgery.

Orpen *et al*. (2006) administered 15mg/kg of tranexamic acid, intravenously, at the time the cement mixing started. Standard thromboprophylaxis was started in all patients in the form of postoperative low-molecular-weight heparin (Fragmin®) subcutaneously, according to existing practice. The drug was administered once a day from the night of surgery until discharge.

Volquind *et al.* (2014) administered 2.5 g of intravenous tranexamic acid, in a single dose, in 0.9% saline solution of 100 mL, five minutes before opening the pneumatic tourniquet. All patients received prophylaxis for deep vein thrombosis with unfractionated heparin at a dose of 5000 IU subcutaneously every eight hours after the first dose applied before insufflation of the pneumatic tourniquet and used compression stockings on both lower limbs for the subsequent seven days. the surgery.

Spanyer *et al.* (2016) administered to all patients 2.0g of topical tranexamic acid (Cyclokapron®) in 40mL of normal saline applied directly to the surgical arthrotomy with the tissues bathed in the solution without disturbance for two minutes at the end of the procedure, before releasing the patient. tourniquet. Chemical DVT prophylaxis was started with low molecular weight heparin in all patients for 14 days after discharge.

Santias *et al*. (2017) treated the group with 2.0 g of topical tranexamic acid (Amchafbrin®) in 50 mL of normal saline (0.9% sodium chloride solution) injected into the knee immediately before skin closure. Thromboembolic prophylaxis was

started with low-molecular-weight heparin, administered for 30 days after discharge.

Huang *et al*. (2017) treated group A (n=50) with a tourniquet as well as intravenous tranexamic acid (20mg/kg) five to ten minutes before the skin incision and three, six, 12, and 24 hours later (10mg/kg) along with 1.0g of topical tranexamic acid in 50mL of normal saline. Topical medication was administered intraoperatively after implantation of the component by means of wound irrigation for five to ten minutes, after which the solution was aspirated. Group B (n=50) was treated in the same way as group A, but without the tourniquet. In both groups, half-dose of enoxaparin (Clexane; 0.2 mL containing 2000 IU) was administered subcutaneously six hours postoperatively and a full dose (0.4 mL containing 4000 IU) was administered at 24-hour intervals until discharge. . After discharge, 10 mg of rivaroxaban was administered orally for ten days if no bleeding events occurred.

Wang *et al*. (2018) treated group B (n=55) with 2.0g of oral tranexamic acid (500 mg, each tablet) two hours preoperatively and then 1.0g of oral medication three hours later, postoperatively. operative and 1g of placebo after seven, 11 and 15 hours postoperatively. Group C (n=55) received 2.0g of oral tranexamic acid after two hours preoperatively and then 1.0g of oral drug after three and seven hours postoperatively, together with 1.0g of placebo after 11 and 15 hours postoperatively. Group D (n=55) received 2.0g of oral tranexamic acid after two hours preoperatively and then 1.0g of oral drug after three, sevem and 11 hours postoperatively, along with 1.0g of placebo after 15 hours postoperatively. Group E (n=55) received 2.0g of oral tranexamic acid after two hours preoperatively and then 1.0g of oral drug after three, seven, 11 and 15 hours postoperatively. All patients received 1.5 g of tranexamic acid diluted in 50 mL of saline administered intra-articularly. All patients also received chemical thromboprophylaxis with low molecular weight heparin. 2000 IU of Clexane was used at the beginning, administered subcutaneously, after eight hours postoperatively and continued once a day (4000 IU) during hospitalization. Finally, Rivaroxaban (10 mg, administered orally) was prescribed for 10 days after discharge.

Zhang *et al*. (2019) did not record postoperative cases of PE and DVT at 6-month follow-up. In all patients, 20mg/kg of tranexamic acid was injected intravenously 15 minutes before tourniquet compression. To stop the bleeding, the tourniquet was loosened and electrical coagulation was used after the prosthesis was installed. A periarticular injection of drug solution (1.0g tranexamic acid, 20ml saline) comprising 5ml for the medial capsule, 5ml for the lateral capsule and 10ml for the soft tissue around the quadriceps femoris. A 20ml tranexamic acid solution (1.0g drug + 20ml saline solution) was injected into the joint cavity after the suture incision. All patients were injected with 1 ml of low molecular weight heparin subcutaneously (Fraxiparin®) on the first day after surgery. After discharge, 10mg of Rivaroxaban (Xarelto®) was administered orally once daily for up to five weeks after the operation.

4. Discussion

The total knee arthroplasty has a growing demand worldwide, due to the aging of the population, (Alves Júnior *et al*., 2010) and the main goals are pain relief and improvement of patient function. Several studies have analyzed the possibility of an increase in thromboembolic events related to the use of tranexamic acid in patients undergoing orthopedic procedures, such as arthroplasty. Due to these complications, a lot of doctors are wary of using this drug. The aim of the present study was to analyze the complications involved in the use of the drug in patients undergoing TKA, specifically regarding the probable occurrence of DVT and PE.

After analyzing the 11 selected articles, a sample of 1.660 submitted to TKA was registered, being 1.135 female (68%) and 525 male (32%). Of these patients, 467 received placebo and 1.193 received tranexamic acid. In the placebo group, seven DVT and no PE were recorded (1.5%); in the treatment group, there were five DVT and one PE (0.5%). Thus, the safety of the use of tranexamic acid is proven, so that 99.5% of the patients did not present thromboembolic events and the index related to positive cases is practically irrelevant, being rare. The likely explanation lies in the fact that tranexamic acid does not affect

fibrinolytic activity in the vein walls and does not promote prothrombotic activity in the groups studied (Lee *et al*., 2017).

Furthermore, arthroplasty presents risks of thrombus formation by the physiological process of coagulation. The mechanisms involved in this process, constituting the hemostatic system, must be regulated to simultaneously counteract excessive blood loss and prevent the formation of intravascular thrombi, resulting from excessive fibrin formation (Franco, 2001). Tranexamic acid, being an antifibrinolytic, promotes greater clot stability. Several studies have reported that the occurrence of thromboembolic events is even higher in patients who do not use acid, as in the article by Zecker *et al*. (2016), in which four deep venous thrombosis were recorded in the group of patients who used placebo and one in the group who used tranexamic acid.

In addition, there is a certain risk group in which the use of tranexamic acid is sought to be avoided, due to the greater probability of thromboembolic events. Spanyer *et al*. (2017) include in the risk group patients with renal failure, those with a history of thromboembolic disorders, such as stroke, myocardial infarction, previous deep vein thrombosis (DVT) or pulmonary embolism (PE). Gali *et al*. (2017) also mention age over 60 years, obesity, use of oral contraceptives or patches, hormone replacement therapy, varicose veins, inflammatory bowel disease and prolonged tourniquet time, if used in arthroplasty (Bin Abd Razak *et al*., 2017).

It is possible to observe that the use of tranexamic acid after total knee arthroplasty is beneficial and effective when combined with prophylactic anticoagulation. An example of this was the study by Razak *et al*. (2016), in which patients did not receive prophylaxis, resulting in seven episodes of DVT and one episode of PE, a considerably higher number than in cases where patients received such prophylaxis (Blanchard *et al*., 1999). Thus, it is assumed that prophylactic anticoagulation reduces thromboembolic events, as seen in the selected articles, where such events occurred less frequently. In addition, studies that did not use such prophylaxis were considered an exclusion criterion, as they raised questions about the origin of thromboembolic events, since they could be the result of the use of tranexamic acid or the non-application of the aforementioned prophylaxis.

Proving the real efficacy of tranexamic acid in the control group, in which placebo was used, in a double-blind study of 557 patients, seven had DVT, a total of approximately 1.5%, a percentage three times higher than in the group in which the drug was used.

Finally, there are some prophylaxis that can be used in this case. There are some studies that compare the efficiency between mechanical and pharmacological methods. Blanchard *et al*. evaluated the occurrence of DVT in 108 patients after TKA, with phlebography performed eight to 12 days after surgery (Blanchard *et al*., 1999). DVT prevention was performed in 60 patients with low molecular weight heparin (LMWH) and, in 48, mechanical prevention was performed with intermittent pneumatic compression of the foot. In this case, 47 episodes of DVT were diagnosed in all patients, 16 (26.7%) in the LMWH group and 31 (64.6%) in the mechanical prophylaxis group. In the study by Volquind *et al*. (2014), in which pharmacological prophylaxis was used (unfractionated heparin 5000 IU subcutaneously every eight hours) associated with the use of compression stockings for seven days in the perioperative period, there was no evidence of thromboembolic events in the patients studied. Therefore, the efficiency of the combined use of mechanical methods with pharmacological prophylaxis is evident.

5. Conclusion

The studies included in this review showed that the majority (99.5%) of the patients did not develop DVT and PTE after the use of tranexamic acid in total knee arthroplasty. Thus, we conclude that the drug is safe and effective to be used in this surgical procedure, in order to minimize the bleeding that is predicted in this case, rarely resulting in thromboembolic events, when not used in the risk group.

Finally, further studies on the proposed topic are recommended, in order to obtain as much scientific evidence as possible and assist physicians in choosing the most appropriate and efficient conduct for total knee arthroplasty.

References

Albuquerque, L., Silveira, F., Zago, A., Bettio, J., Petracco, J., & Alegre, P. (1997). Terapia Trombolítica em Trombose Venosa Profunda. Experiência Clínica Inicial Comunicações Breves. *Arq Bras Cardiol*, 68(2), 125–128. http://publicacoes.cardiol.br/abc/1997/6802/68020011.pdf

Alves Júnior, W. M., Migon, E. Z., & Zabeu, J. L. A. (2010). Dor no joelho após artroplastia total - uma abordagem sistematizada. *Revista Brasileira de Ortopedia*, 45, 384–391. https://doi.org/10.1590/S0102-36162010000500002

Bin Abd Razak, H. R., Binte Abd Razak, N. F., & Tan, H.-C. A. (2017). Prevalence of Venous Thromboembolic Events Is Low in Asians After Total Knee Arthroplasty Without Chemoprophylaxis. *The Journal of Arthroplasty*, 32(3), 974–979. https://doi.org/10.1016/j.arth.2016.09.008

Blanchard, J., Meuwly, J. Y., Leyvraz, P. F., Miron, M. J., Bounameaux, H., Hoffmeyer, P., Didier, D., & Schneider, P. A. (1999). Prevention of deep-vein thrombosis after total knee replacement. Randomised comparison between a low-molecular-weight heparin (nadroparin) and mechanical prophylaxis with a foot-pump system. *The Journal of Bone and Joint Surgery. British Volume*, 81(4), 654–659. https://doi.org/10.1302/0301-620x.81b4.9464

Boström, J., Grant, J. A., Fjellström, O., Thelin, A., & Gustafsson, D. (2013). Potent Fibrinolysis Inhibitor Discovered by Shape and Electrostatic Complementarity to the Drug Tranexamic Acid. *Journal of Medicinal Chemistry*, 56(8), 3273–3280. https://doi.org/10.1021/jm301818g

Bredbacka, S., Andreen, M., Blombäck, M., & Wykman, A. (1987). Activation of cascade systems by hip arthroplasty. No difference between fixation with and without cement. *Acta Orthopaedica Scandinavica*, 58(3), 231–235. https://doi.org/10.3109/17453678709146472

Eriksson, B. I., Eriksson, E., Gyzander, E., Teger-nilsson, A.-C., & Risberg, B. (1989). Thrombosis after hip replacement: Relationship to the fibrinolytic system. *Acta Orthopaedica Scandinavica*, 60(2), 159–163. https://doi.org/10.3109/17453678909149244

Francis, C. W., Ricotta, J. J., Evarts, C. M., & Marder, V. J. (1988). Long-term clinical observations and venous functional abnormalities after asymptomatic venous thrombosis following total hip or knee arthroplasty. *Clinical Orthopaedics and Related Research*, 232, 271–278. https://pubmed.ncbi.nlm.nih.gov/3383492/

Franco, R. F. (2001). Fisiologia da coagulação, anticoagulação e fibrinólise. *Medicina (Ribeirão Preto)*, 34(3/4), 229–237. https://doi.org/10.11606/issn.2176-7262.v34i3/4p229-237

Gali, J., & Camargo, D. (2019). Tromboprofilaxia na artroplastia total do joelho. *Revista Brasileira de Ortopedia*, 54(01), 001–005. https://doi.org/10.1016/j.rbo.2017.06.025

Huang, Z., Xie, X., Li, L., Huang, Q., Ma, J., Shen, B., Kraus, V. B., & Pei, F. (2017). Intravenous and Topical Tranexamic Acid Alone Are Superior to Tourniquet Use for Primary Total Knee Arthroplasty: A Prospective, Randomized Controlled Trial. *The Journal of Bone and Joint Surgery*. American Volume, 99(24), 2053–2061. https://doi.org/10.2106/JBJS.16.01525

Jansen, A. J., Andreica, S., Claeys, M., D'Haese, J., Camu, F., & Jochmans, K. (1999). Use of tranexamic acid for an effective blood conservation strategy after total knee arthroplasty. *British Journal of Anaesthesia*, 83(4), 596–601. https://doi.org/10.1093/bja/83.4.596

Jeter, E. K., & Spivey, M. A. (1995). Noninfectious Complications of Blood Transfusion. *Hematology/Oncology Clinics of North America*, 9(1), 187–204. https://doi.org/10.1016/s0889-8588(18)30116-3

Lee, S. Y., Chong, S., Balasubramanian, D., Na, Y. G., & Kim, T. K. (2017). What is the Ideal Route of Administration of Tranexamic Acid in TKA? A Randomized Controlled Trial. *Clinical Orthopaedics & Related Research*, 475(8), 1987–1996. https://doi.org/10.1007/s11999-017-5311-z

Morales Santias, M., Mas Martinez, J., Sanz-Reig, J., Martínez Gimenez, E., Verdu Román, C., & Bustamante Suarez de Puga, D. (2020). Topical tranexamic acid in cemented primary total knee arthroplasty without tourniquet: a prospective randomized study. *European Journal of Orthopaedic Surgery & Traumatology*, 30(6), 1003–1008. https://doi.org/10.1007/s00590-020-02656-9

Orpen, N. M., Little, C., Walker, G., & Crawfurd, E. J. P. (2006). Tranexamic acid reduces early post-operative blood loss after total knee arthroplasty: A prospective randomised controlled trial of 29 patients. *The Knee*, 13(2), 106–110. https://doi.org/10.1016/j.knee.2005.11.001

Padala, P., Rouholamin, E., & Mehta, R. (2010). The Role of Drains and Tourniquets in Primary Total Knee Replacement – A Comparative Study of TKR Performed With Drains and Tourniquet Versus No Drains and Adrenaline and Saline Infiltration. *The Journal of Knee Surgery*, 17(01), 24–27. https://doi.org/10.1055/s-0030-1247143

Roy, N., Smith, M., Anwar, M., & Elsworth, C. (2006). Delayed release of drain in total knee replacement reduces blood loss. A prospective randomised study. *Acta Orthopaedica Belgica*, 72(1), 34–38. https://pubmed.ncbi.nlm.nih.gov/16570892/

Silva, C. C., Savian, C. M., Prevedello, B. P., Zamberlan, C., Dalpian, D. M., & Santos, B. Z. dos. (2020). Access and use of dentalservices by pregnant women: An integrative literature review. *Ciencia e Saude Coletiva*, 25(3), 827–835.https://doi.org/10.1590/1413-81232020253.01192018

Souza, M. T., Silva, M. D., & Carvalho, R. (2010). Integrative review: what is it? How to do it? *Einstein (São Paulo)*,8(1), 102–106.https://doi.org/10.1590/s1679-45082010rw1134

Spanyer, J., Patel, J., Emberton, E., Smith, L., & Malkani, A. (2016). Topical Tranexamic Acid in Total Knee Arthroplasty Patients with Increased Thromboembolic Risk. *The Journal of Knee Surgery*, 30(05), 474–478. https://doi.org/10.1055/s-0036-1593371

Tille, E., Mysliwietz, J., Beyer, F., Postler, A., & Lützner, J. (2019). Intraarticular use of tranexamic acid reduces blood loss and transfusion rate after primary total knee arthroplasty. *BMC Musculoskeletal Disorders*, 20(1). https://doi.org/10.1186/s12891-019-2715-9

Volquind, D., Zardo, R. A., Winkler, B. C., Londero, B. B., Zanelatto, N., & Leichtweis, G. P. (2016). Uso do ácido tranexâmico em artroplastia total primária de joelho: repercussões na perda sanguínea perioperatória. *Brazilian Journal of Anesthesiology*, 66(3), 254–258. https://doi.org/10.1016/j.bjan.2014.11.002

Wang, D., Luo, Z.-Y., Yu, Z.-P., Liu, L.-X., Chen, C., Meng, W.-K., Yu, Q.-P., Pei, F.-X., Zhou, Z.-K., & Zeng, W.-N. (2018). The antifibrinolytic and anti-inflammatory effects of multiple doses of oral tranexamic acid in total knee arthroplasty patients: a randomized controlled trial. *Journal of Thrombosis and Haemostasis*, 16(12), 2442–2453. https://doi.org/10.1111/jth.14316

Zekcer, A., Del Priori, R., Tieppo, C., Silva, R. S. da, & Severino, N. R. (2016). Topical vs. intravenous administration of tranexamic acid in knee arthroplasty and prevalence of deep venous thrombosis: a randomized clinical trial. *Jornal Vascular Brasileiro*, 15(2), 120–125. https://doi.org/10.1590/1677-5449.007515

Zhang, S., Wang, C., Shi, L., & Xue, Q. (2019). Multi-route applications of tranexamic acid to reduce blood loss after total knee arthroplasty. *Medicine*, 98(30), e16570. https://doi.org/10.1097/md.0000000000016570