



Original article

Evaluation of the use of tranexamic acid in total knee arthroplasty[☆]



Mariana Diana Chaves de Almeida^a, Rodrigo Pires e Albuquerque^{a,*},
Guilherme Mathias Palhares^a, Juliana Patrícia Chaves de Almeida^b,
João Mauricio Barretto^a, Naasson Cavanellas^a

^a Centro de Cirurgia do Joelho, Instituto Nacional de Traumatologia e Ortopedia (Into), Rio de Janeiro, RJ, Brazil

^b Hospital Federal da Lagoa, Rio de Janeiro, RJ, Brazil

ARTICLE INFO

Article history:

Received 12 May 2017

Accepted 20 June 2017

Available online 19 September 2018

Keywords:

Tranexamic acid

Bleeding

Orthopedic

Total knee arthroplasty

Blood transfusion

Blood volume

ABSTRACT

Objective: Evaluate the efficacy of tranexamic acid in reducing bleeding in patients undergoing total knee arthroplasty.

Methods: 101 patients were randomized into two groups: the tranexamic acid group ($n = 51$) and the placebo group ($n = 50$). Patients were compared regarding the following parameters: reduction of hemoglobin, total estimated blood loss, drain output, and postoperative blood transfusion rate.

Results: Comparing the groups, there were statistically significant differences ($p < 0.05$) in the following parameters: reduction of hemoglobin, decreased hematocrit, estimated blood loss, and drain output. All values were lower in the tranexamic acid group. Only placebo group patients required blood transfusion.

Conclusion: The use of intravenous tranexamic acid is effective to reduce bleeding in patients undergoing total knee arthroplasty.

© 2017 Sociedade Brasileira de Ortopedia e Traumatologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Avaliação do uso do ácido tranexâmico em artroplastia total do joelho

RESUMO

Objetivo: Avaliar a eficácia do ácido tranexâmico na redução do sangramento em pacientes submetidos a artroplastia total de joelho.

Métodos: Foram randomizados 101 pacientes em dois grupos: grupo ácido tranexâmico ($n = 51$) e grupo placebo ($n = 50$). Os pacientes foram comparados nos quesitos redução da hemoglobina, perda sanguínea total estimada, débito do dreno e taxa de hemotransfusão pós-operatória.

Palavras-chave:

Ácido tranexâmico

Sangramento

Ortopedia

Artroplastia do joelho

Transfusão de sangue

Volume sanguíneo

[☆] Study conducted at Centro de Cirurgia do Joelho, Instituto Nacional de Traumatologia e Ortopedia (INTO), Rio de Janeiro, RJ, Brazil.

* Corresponding author.

E-mail: rodalbuquerque19@gmail.com (R.P. Albuquerque).

<https://doi.org/10.1016/j.rboe.2018.09.008>

2255-4971/© 2017 Sociedade Brasileira de Ortopedia e Traumatologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Resultados: Na comparação entre os grupos, observou-se diferença estatística ($p < 0,05$) nos seguintes parâmetros: redução da hemoglobina, redução do hematócrito, perda sanguínea estimada e débito do dreno. Todos os valores foram menores no grupo do ácido tranexâmico. Somente pacientes do grupo placebo necessitaram de hemotransfusão.

Conclusão: O uso de ácido tranexâmico intravenoso é eficaz para reduzir o sangramento dos pacientes submetidos a artroplastia total de joelho.

© 2017 Sociedade Brasileira de Ortopedia e Traumatologia. Publicado por Elsevier Editora Ltda. Este é um artigo Open Access sob uma licença CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The main indication for total knee arthroplasty (TKA) is the final treatment of cases of severe knee osteoarthritis.¹ TKA is considered to be one of the orthopedic surgeries with the highest estimated bleeding,² with values ranging from 300 to 2000 ml.³ Several studies show a high incidence of transfusion in the postoperative period^{2,4}; according to Wong et al.,⁵ these rates vary from 10% to 38%.

Homologous transfusions are associated with prolonged hospitalization and increased costs, as well as with increased morbidity and mortality^{3,4} due to the large number of complications related to the procedure, such as an increase in the incidence of wound infections,^{3,4} fluid overload, increased hospitalization time,^{3,4} viral infections, immunodepression, hemolytic reactions, and inflammatory tissue lesions,⁶ in addition to the inherent risks of HIV and hepatitis C infection, among other bloodborne diseases.

Autotransfusion (autologous) with pre-drawn blood through a blood storage system has been advocated in TKAs, in an attempt to avoid the complications of homologous transfusions.⁷ However, autologous transfusions are expensive, not without complications,^{3,4} and cannot always be used in elderly patients.²

In order to reduce the number of blood transfusions in TKA, some precautions are taken to try to minimize perioperative and postoperative bleeding, such as occlusion of the femoral intramedullary canal with bone graft,⁸ use of pneumatic tourniquet and suction drain,^{3,4} improvement of surgical technique,³ anesthesia combined with hypotension,⁹ cryotherapy and Jones bandage,¹⁰ postoperative drainage clamping,¹¹ local application of fibrin glue,¹² use of tranexamic acid,¹³ local infusion with norepinephrine,¹⁴ and the placement of platelet gel in the operative wound.¹⁵

The widespread use of tranexamic acid in bleeding control is well established in several surgical specialties, such as gynecology¹⁶ and cardiac surgery.¹⁷ Its use in orthopedic surgery has generally demonstrated similar efficacy.¹⁸

The antifibrinolytic effect of tranexamic acid is due to the reversible formation of the tranexamic acid-plasminogen complex, which eventually slows fibrinolysis and preserves the previously formed clot.^{3,4}

The present study was conducted to corroborate the literature data and possibly establish the regular use of the medication as a protocol in this hospital.

The main objective of the study was to determine the efficacy of tranexamic acid in reducing bleeding in TKA, as well as to evaluate its impact on patients' transfusion requirements.

Material and methods

This was a prospective, randomized, triple-blinded study (patient, surgical team, data collection team), previously approved by the Ethics and Research Committee of this institution and submitted to the Brazil Platform under the number CAAE 36137314.3.0000.5273.

Patients with primary knee osteoarthritis who underwent TKA were selected. All patients underwent spinal anesthesia associated with femoral and sciatic nerves peripheral block. The surgeries were performed under ischemia with a pneumatic cuff inflated to a pressure 125 mmHg higher than the patient's systolic blood pressure after limb exsanguination. All surgeries were performed with the patient in the supine position through the classical medial parapatellar approach; in all cases, the Hemovac[®] drain was removed 24 h after the procedure, and its output was recorded. In all patients, post-stabilized Press Fit Condylar Sigma (PFC sigma/DePuy-Synthes[®]) implants with patellar replacement were used. All surgeries were performed by surgeons from this hospital group from September 2014 to January 2015.

Patients of both genders with primary knee osteoarthritis admitted to the hospital for TKA were selected to participate in this study. Prior to joining the study, all patients received clarifications, in simple and clear language, regarding the benefits and risks of treatment. After showing understanding of what was proposed, the patient or their legal representative signed the Informed Consent Form.

The exclusion criteria were previous surgery in the same joint, evidence of joint infection, patients with congenital or acquired coagulopathies, active intravascular coagulation, acute occlusive vasculopathy, hypersensitivity to components of the Transamin[®] formula, chronic use of oral anticoagulants and corticosteroids, history of severe or moderate allergy to plasma transfusion, patients with chronic heart disease, patients with malignant neoplasms and autoimmune diseases, major bone defects requiring bone grafting, and knee arthroplasty revision surgeries, as well as not agreeing to sign the Informed Consent Form.

Table 1 – Comparability between control and intervention groups regarding anthropometric variables prior to surgery.

| Variables | Control (n = 50) Mean | Tranexamic acid (n = 51) Mean | Student's t-test p-value |
|--------------------------------|--------------------------|----------------------------------|-----------------------------|
| Age (years) | 68.5 | 66.6 | 0.1377 |
| Weight (kg) | 78.8 | 76.6 | 0.3477 |
| Height (m) | 1.60 | 1.58 | 0.2334 |
| Blood volume (l) | 4.4 | 4.2 | 0.2517 |
| Preoperative hemoglobin (g/dl) | 14.1 | 13.5 | 0.0193 |
| Preoperative hematocrit (%) | 42.2 | 40.3 | 0.0092 |
| TAP (%) | 98.6 | 97.5 | 0.2767 |
| Female gender - n (%) | 34 (48.6) | 36 (51.4) | 0.778 ^a |

^a Chi-squared test.

The patients were randomized into two groups: tranexamic acid (intervention) and placebo (control). As this was a randomized, controlled, triple-blinded study, neither the patient nor the surgeon or members of the team were aware of the group to which the operated patient belonged. Patients were randomized to the tranexamic acid or placebo group using opaque, sealed envelopes. For the randomization, 55 envelopes with a card with the word “medicine” and 55 envelopes with a card with the word “placebo” were made. The envelopes were opened by the anesthesiologist after the end of the blockades and before the pneumatic cuff was inflated. The medication or placebo was then administered, five minutes before the onset of ischemia. The surgeon was not informed of the contents of the drawn envelope.

After randomization, the final sample consisted of 101 patients, 70 females and 31 males, ranging from 52 to 85 years. Table 1 shows the comparison between groups.

Nine patients were excluded from the study, four from the intervention group and five from the placebo group because they met the exclusion criteria: two did not undergo patellar replacement and seven had contraindications to the drug.

The patients belonging to the tranexamic acid group received a standardized dose of 1 g of the drug, divided into four 5 ml ampoules of 250 mg each before the pneumatic cuff was inflated. In the control group, placebo was applied in the same manner. All surgical procedures were performed in accordance with the protocols established in the hospital routine. The only injectable form of tranexamic acid available in the hospital is manufactured by the NIKKHO laboratory, under

the brand name of Transamin[®]. The placebo used was 0.9% saline solution.

The following parameters were considered individually in all patients in the analysis and calculation of total blood loss. The complete blood count measured on the day before the surgery was compared with that on the first postoperative day. A preoperative coagulogram was performed to evaluate the possible intervention of the index values in the final postoperative bleeding volume. The 24-h drain output was recorded for all patients. Patients' weight, height, and gender were also considered.

Blood loss was calculated based on hemoglobin levels, adjusted to the patient's blood volume.^{19,20} The calculation of volume (l) was stratified by genders. Women: $(\text{height}^3 \times 0.3561) + (\text{weight} \times 0.03308) + 0.1833$ and men: $(\text{height}^3 \times 0.3666) + (\text{weight} \times 0.3219) + 0.6041$. The following parameters were also observed: hemoglobin reduction, hematocrit reduction, mean hematocrit, total blood loss (blood volume \times [hematocrit reduction/mean hematocrit]), and number of transfusions.

The data were tabulated in a spreadsheet for statistical analysis and comparison among the selected variables. The significance criterion adopted was the level of 5%, i.e., when the p-value of the statistical test is less than or equal to 0.05, there is statistical significance. The statistical analysis was performed using the statistical software Stata version 12.1.

In the statistical analysis for comparison of quantitative data between two groups (control and intervention), Student's t-test for independent samples was used, since the variables

Table 2 – Comparison of red cells indexes before and after surgery between control and intervention groups.

| Red cells indexes | Control (n = 50) Mean | Tranexamic acid (n = 51) Mean (SD) | Student's t-test p-value |
|-----------------------------|--------------------------|---------------------------------------|-----------------------------|
| Hemoglobin reduction (g/dl) | 3.2 | 2.2 | 0.0007 |
| Hematocrit reduction (%) | 9.8 | 7.1 | 0.0031 |
| Blood volume loss (l) | 1.2 | 0.8 | 0.0038 |
| Drain output (ml) | 352.6 | 189.3 | 0.0012 |

A statistically significant difference was observed in all indices.

presented normal distribution (Gaussian distribution) verified by the q-q plot. To compare qualitative data, the chi-squared test (χ^2) was applied.

Results

When comparing the preoperative mean hemoglobin and hematocrit values, a statistically significant difference was observed between the two groups; the value was lower in the group that received the drug. However, despite the significant difference, these mean values did not present a clinical difference, as they were within the parameters of laboratory normality.

As to the other analyzed criteria, the results did not present a significant difference, which indicates that both groups are homogeneous and comparable.

When compared with those in the control group, patients in the intervention (tranexamic acid) group presented statistically significant lower rates of hemoglobin and hematocrit reduction in the postoperative values when compared with the baseline values, as well as a significant reduction in apparent bleeding (24-h drain output) and estimated bleeding (blood loss volume calculation). [Table 2](#) summarizes the statistical analysis of the present results, demonstrating statistical significance in all parameters evaluated.

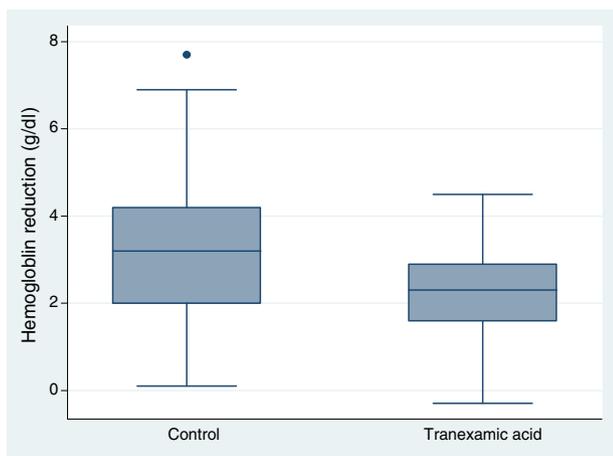


Fig. 1 – Box plot of hemoglobin reduction results. The central line of each group represents its median and the rectangles (boxes) represent 50% of the patients in each group, comprised between the first and third quartiles. The lines that leave the boxes determine the upper and lower margins of the “typical” results found in each group. The point found in the control group is an outlier. Control group: minimum value = 0.1; maximum value = 7.7; first quartile = 2.0; third quartile = 4.2; median = 3.2. Tranexamic acid group: minimum value = -0.3; maximum value = 4.5; first quartile = 1.6; third quartile = 2.9; median = 2.3.

The results of the control group showed greater variability, while the results of the tranexamic acid group presented greater homogeneity. The results of each parameter evaluated are also individually represented in box-plot diagrams (Figs. 1–4).

In the control group, six patients underwent blood transfusion. No transfusions were performed in patients who used tranexamic acid.

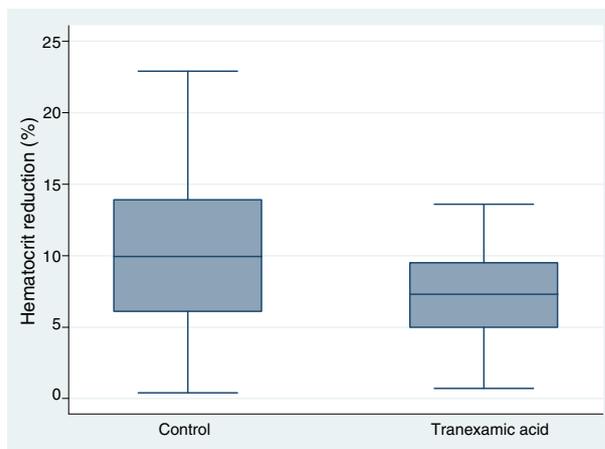


Fig. 2 – Box plot of hematocrit reduction results (%). Control group: minimum value = 0.4; maximum value = 22.9; first quartile = 6.1; third quartile = 13.9; median = 9.9. Tranexamic acid group: minimum value = 0.7; maximum value = 13.6; first quartile = 5.0; third quartile = 9.5; median = 7.3.

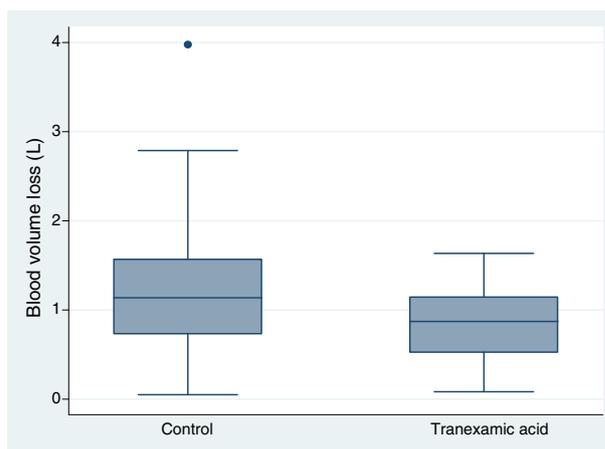


Fig. 3 – Box plot of estimated blood volume loss (L). Control group: minimum value = 0.1; maximum value = 4.0; first quartile = 0.7; third quartile = 1.6; median = 1.1. One outlier was observed in this group. Tranexamic acid group: minimum value = 0.1; maximum value = 1.6; first quartile = 0.5; third quartile = 1.1; median = 0.9.

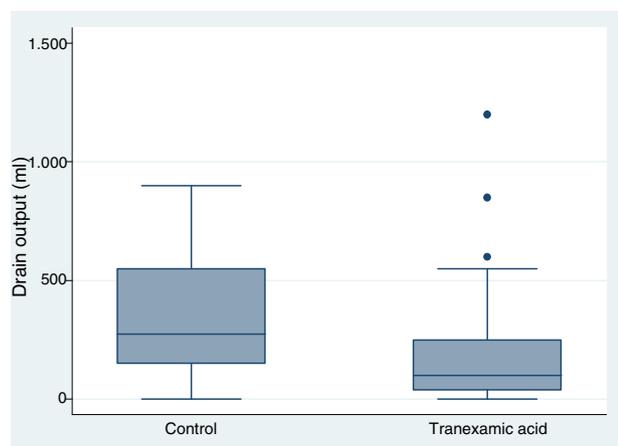


Fig. 4 – Box plot of the drain output comparison (ml). Control group: minimum value = 0.0; maximum value = 900; first quartile = 150; third quartile = 550; median = 275. Tranexamic acid group: minimum value = 0.0; maximum value = 1200; first quartile = 40; third quartile = 250; median = 100. Three outliers were observed in this group.

Discussion

Currently, approximately 450,000 TKAs are performed annually in the United States.²¹ The satisfactory results found in the literature, the improvement of the technique, and the aging of the population have stimulated an increase in the number of procedures.²² Kurtz et al.²³ estimate an increase of about 670% in the number of TKAs; by 2030, approximately 3.5 million procedures will have been performed annually in the United States alone. The high blood loss³ and consequently the high transfusion rate⁵ lead to an increase in hospital admission costs.³ With the prospect of an increased number of surgeries to be performed annually, a significant economic impact from hospital costs is expected. The mean value of only one unit of red blood cells in the United States is USD 950²⁴ and one ampoule of tranexamic acid costs USD 6.⁵ It is expected that the reduction of bleeding through the use of tranexamic acid will bring savings to the healthcare system, reinforcing the importance of the present study.

The venous application of tranexamic acid was chosen based on several studies that have demonstrated an efficacy similar or superior to the topical application.^{25,26} It also allowed the surgical team to be blinded to the group to which the patient belonged. Intravenous administration of tranexamic acid has the advantage of being faster; it is not necessary to await the effect of the medication, a characteristic of the topical method.¹³ Similarly, the literature is not clear regarding the effects of tranexamic acid applied topically in contact with bone or muscle tissue¹³; Furthermore, there is no consensus on the concentration in the topical application.²⁷ Therefore, the authors opted to assess only the intravenous administration of this drug associated with a control group.

The standardization of a single 1g IV dose in the present study, as well as the results observed, are similar to the findings by Levine et al.²⁸

Venous tranexamic acid has severe contraindications in patients with previous history of deep vein thrombosis, renal insufficiency, heart disease, or cerebrovascular disease,⁴ therefore, making a good preoperative clinical evaluation and a preanesthesia consultation essential. In this way, it is possible to minimize errors in the indication of this drug and prevent possible complications. The present study excluded a small number of patients due to a good anamnesis performed in the preoperative period. The authors emphasize that the preoperative evaluation by the multidisciplinary team increases the safety in the use of this drug.

Tzatzairis et al.²⁷ indicated that tranexamic acid can be used in patients who undergo TKA without a pneumatic cuff. The present authors consider that the pneumatic cuff can be routinely used during knee replacement surgery. The advantages of its use are that it promotes a cleaner operative field, reduces perioperative bleeding, improves the quality of implant cementation, and reduces the duration of surgery,²⁹ besides reducing the risk of the surgeon acquiring diseases transmissible from biological accidents.²⁹ In the present study, the pneumatic cuff was used in all cases.

In this study, the use of tranexamic acid IV was effective in minimizing bleeding in TKA, which corroborates the findings of Alshryda et al.²⁵ and Seo et al.,²⁶ with a significant decrease in estimated blood loss and reduction of red cells indexes. In the comparison between the groups, the parameter that presented the greatest disparity was the apparent bleeding, represented by the measurement of the drain output.

Patients in the intervention (tranexamic acid) group presented a more uniform pattern, with more homogeneous results due to the drug action. As they were not influenced by the use of acid, the results of the control (placebo) group were more heterogeneous, with greater susceptibility to other variables of minor importance, such as gender, age, weight, blood volume, and preoperative prothrombin activation time, whose influences on final bleeding were not individualized, since the groups were homogenous regarding the distribution of the characteristics.

The fact that blood transfusion was required in six patients in the control group and in none of the patients in the intervention group demonstrates a lower tendency for transfusion in the cases that used tranexamic acid, which is consistent with the expected result of the use of this drug.¹³

The present study shows as a limitation the fact that patients were not followed-up during the late postoperative period to evaluate the incidence of complications in the groups and the comparison between them. This is because the safety of the use of tranexamic acid has already been demonstrated in a meta-analysis by Zhang et al.,³⁰ who did not observe an increase in complications between patients who used the drug and patients who underwent TKA without its use.

According to the above results, it was observed that the perioperative administration of tranexamic acid in a single dose of 1 g is effective to significantly reduce the hematometric indexes in the postoperative period, in addition to reducing drain output and estimated bleeding volume, which resulted in a lower blood transfusion rate in patients submitted to TKA.

Conclusion

The use of intravenous tranexamic acid was effective in reducing bleeding in patients undergoing TKA.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

- Diduch DR, Insall JN, Scott WN, Scuderi GR, Font-Rodriguez D. Total knee replacement in young, active patients, long-term follow-up and functional outcome. *J Bone Joint Surg Am.* 1997;79(4):575-82.
- Berman AT, Geissele AE, Bosacco SJ. Blood loss with total knee arthroplasty. *Clin Orthop Relat Res.* 1988;(234):137-8.
- 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.
- Liu D, Dan M, Martinez Martos S, Beller E. Blood management strategies in total knee arthroplasty. *Knee Surg Relat Res.* 2016;28(3):179-87.
- 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.
- Volpato SE, Ferreira JS, Ferreira VL, Ferreira DC. Transfusão de concentrado de hemácias em unidade de terapia intensiva. *Rev Bras Hematol Hemoter.* 2005;27:179-82.
- Malta MC, Motta Filho G, Barretto JM, Santos MA. Incidência de hemotransfusão na artroplastia total primária unilateral do joelho. *Rev Bras Ortop.* 2000;35(10):416-8.
- Kumar N, Saleh J, Gardiner E, Devadoss VG, Howell FR. Plugging the intramedullary canal of the femur in total knee arthroplasty: reduction in postoperative blood loss. *J Arthroplasty.* 2000;15(7):947-9.
- Juelsgaard P, Larsen UT, Sørensen JV, Madsen F, Søballe K. Hypotensive epidural anesthesia in total knee replacement without tourniquet: reduced blood loss and transfusion. *Reg Anesth Pain Med.* 2001;26(2):105-10.
- Gibbons CE, Solan MC, Ricketts DM, Patterson M. Cryotherapy compared with Robert Jones bandage after total knee replacement: a prospective randomized trial. *Int Orthop.* 2001;25(4):250-2.
- Roy N, Smith M, Anwar M, Elsworth C. Delayed release of drain in total knee replacement reduces blood loss. A prospective randomised study. *Acta Orthop Belg.* 2006;72(1):34-8.
- Wang GJ, Hungerford DS, Savory CG, Rosenberg AG, Mont MA, Burks SG, et al. Use of fibrin sealant to reduce bloody drainage and hemoglobin loss after total knee arthroplasty: a brief note on a randomized prospective trial. *J Bone Joint Surg Am.* 2001;83(10):1503-5.
- Sadigurski D, Andion D, Boureau P, Ferreira MC, Carneiro RJF, Colavolpe PO. Efeito do ácido tranexâmico na prevenção do sangramento na artroplastia total de joelho. *Acta Ortop Bras.* 2016;24(3):131-6.
- Gasparini G, Papaleo P, Pola P, Cerciello S, Pola E, Fabbriani C. Local infusion of norepinephrine reduces blood losses and need of transfusion in total knee arthroplasty. *Int Orthop.* 2006;30(4):253-6.
- Gardner MJ, Demetropoulos D, Klepchick PR, Mooar PA. The efficacy of autologous platelet gel in pain control and blood loss in total knee arthroplasty. An analysis of the haemoglobin, narcotic requirement and range of motion. *Int Orthop.* 2007;31(3):309-13.
- Wellington K, Wagstaff AJ. Tranexamic acid: a review of its use in the management of menorrhagia. *Drugs.* 2003;63(13):1417-33.
- Mongan PD, Brown RS, Thwaites BK. Tranexamic acid and aprotinin reduce postoperative bleeding and transfusions during primary coronary revascularization. *Anesth Analg.* 1998;87(2):258-65.
- Shapiro F, Zurakowski D, Sethna NF. Tranexamic acid diminishes intraoperative blood loss and transfusion in spinal fusions for duchenne muscular dystrophy scoliosis. *Spine (Phila Pa 1976).* 2007;32(20):2278-83.
- Gross JB. Estimating allowable blood loss: corrected for dilution. *Anesthesiology.* 1983;58(3):277-80.
- 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.
- Healthcare Cost and Utilization Project (HCUP). HCUP facts and figures: statistics on hospital-based care in the United States, 2007 [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2009. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK53001/>.
- Ritter MA. The anatomical graduated component total knee replacement: a long-term evaluation with 20-year survival analysis. *J Bone Joint Surg Br.* 2009;91(6):745-9.
- Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am.* 2007;89(4):780-5.
- Shander A, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn DR. Activity-based costs of blood transfusions in surgical patients at four hospitals. *Transfusion.* 2010;50(4):753-65.
- Alshryda S, Mason J, Vaghela M, Sarda P, Nargol A, Maheswaran S, et al. Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total knee replacement: a randomized controlled trial (TRANX-K). *J Bone Joint Surg Am.* 2013;95(21):1961-8.
- Seo JG, Moon YW, Park SH, Kim SM, Ko KR. The comparative efficacies of intra-articular and IV tranexamic acid for reducing blood loss during total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc.* 2013;21(8):1869-74.
- Tzatzairis TK, Drosos GI, Kotsios SE, Ververidis AN, Vogiatzaki TD, Kazakos KI. Intravenous vs topical tranexamic acid in total knee arthroplasty without tourniquet application: a randomized controlled study. *J Arthroplasty.* 2016;31(11):2465-70.
- Levine BR, Haughom BD, Belkin MN, Goldstein ZH. Weighted versus uniform dose of tranexamic acid in patients undergoing primary, elective knee arthroplasty: a prospective randomized controlled trial. *J Arthroplasty.* 2014;29 9 Suppl:186-8.

-
29. Vivacqua T, Barroso M, Matos P, Albuquerque RP, Cavanellas N, Barretto JM. O uso do manguito pneumático em pacientes submetidos a artroplastia total do joelho com ou sem calcificação da artéria poplítea [internet]. Rev Bras Ortop. 2017, <http://dx.doi.org/10.1016/j.rbo.2016.12.005>.
30. Zhang H, Chen J, Chen F, Que W. The effect of tranexamic acid on blood loss and use of blood products in total knee arthroplasty: a meta-analysis. *Knee Surg Sports Traumatol Arthrosc.* 2012;20(9):1742-52.