SOCIEDADE BRASILEIRA DE ORTOPEDIA E TRAUMATOLOGIA

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Original Article

The use of tranexamic acid in patients submitted to primary total hip arthroplasty: an evaluation of its impact in different administration protocols☆

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ARTICLE INFO

Article history:
Received 30 November 2016
Accepted 26 January 2017
Available online 29 July 2017

Keywords:
Hip arthroplasty
Tranexamic acid
Hemotransfusion

ABSTRACT

Objectives: There is still no consensus as to the best form and dosages of use of tranexamic acid. The aim of this study was to evaluate the use of tranexamic acid in total hip arthroplasty, in order to reduce blood loss and decrease hemoglobin, taking into account different administration protocols.

Methods: 42 patients submitted to total hip arthroplasty were divided into three groups. The study was prospective and randomized. Group 1 received a venous dose of tranexamic acid of 15 mg/kg, 20 min prior to bolus incision. Group 2 received an intravenous dose of 15 mg/kg bolus, 20 min before the incision, and an extra dose of 10 mg/kg by infusion pump during the duration of the surgical procedure. Patients in group 3 did not receive tranexamic acid, being the control group. Pre- and post-operative hemoglobin levels were measured and blood loss was measured 24 h after surgery using a Portovac drain.

Results: There was a significant reduction in the amount of bleeding through the Portovac drain and reduction in postoperative hemoglobin drop in patients who used tranexamic acid. There was neither significant difference in hemoglobin drop between groups 1 and 2, nor was there a need for hemotransfusion. Two patients in group 3 required blood transfusion.

Conclusions: The findings demonstrated that the use of intravenous tranexamic acid in total hip arthroplasty reduced postoperative bleeding rates and significantly reduced serum hemoglobin without increasing thromboembolic effects. The bolus and bolus + infusion pump methods were shown to have a similar influence on hemoglobin and need for blood transfusion.

☆ Study conducted at Rede Mater Dei de Saúde, Belo Horizonte, MG, Brazil.

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http://dx.doi.org/10.1016/j.rboe.2017.07.004

O uso do ácido tranexâmico em pacientes submetidos a artroplastia total primária do quadril: uma avaliação do seu impacto em diferentes protocolos de administração

Palavras-chave:
Artroplastia de quadril
Ácido tranexâmico
Hemotransfusão

RESUMO

Objetivos: Ainda não há consenso sobre qual a melhor forma e quais as dosagens de uso do ácido tranexâmico. O objetivo do estudo foi avaliar o uso do ácido tranexâmico na artroplastia total do quadril quanto à redução da perda sanguínea e queda de hemoglobina. Levaram-se em consideração diferentes protocolos de administração.

Métodos: Foram divididos em três grupos 42 pacientes submetidos à artroplastia total do quadril. O estudo foi prospectivo e randomizado. O grupo 1 recebeu uma dose venosa de ácido tranexâmico de 15 mg/kg 20 minutos antes de incisão, em bólus. O grupo 2 recebeu uma dose endovenosa de 15 mg/kg em bólus, 20 minutos antes da incisão, e uma dose extra de 10 mg/kg através de bomba de infusão durante a duração do procedimento cirúrgico. Os pacientes do grupo 3 – controle – não receberam ácido tranexâmico. Foram feitas dosagens de hemoglobina pré e pós-operatoriamente e foi medida a perda sanguínea em 24 horas após a cirurgia através do uso de dreno portovac.

Resultados: Houve uma redução significativa na quantidade de sangramento através do dreno portovac e redução na queda da hemoglobina pós-operatória nos pacientes que usaram ácido tranexâmico. Não houve diferença significativa na queda de hemoglobina entre os grupos 1 e 2, assim como não houve necessidade de hemotransfusão. Dois pacientes do grupo 3 necessitaram de hemotransfusão.

Conclusões: Os achados demonstraram que o uso do ácido tranexâmico por via endovenosa na artroplastia total do quadril reduziu as taxas de sangramento no pós-operatório e queda da hemoglobina sérica de forma significativa, sem aumentar os efeitos tromboembólicos. Os métodos bólus e bólus + bomba de infusão demonstraram ter uma influência semelhante quanto à hemoglobina, perda sanguínea através dos drenos e necessidade de hemotransfusão.

Introduction

Total hip arthroplasty (THA) has become an excellent treatment method for pain relief and functional improvement in patients with degenerative hip joint disease. Initially, its indication was restricted to elderly patients with lower functional demands. However, surgical technique improvements and the evolution of implants and its friction surfaces, which provide less wear and tear, have widened the universe of patients who could benefit from this procedure.[1]

Perioperative blood loss is a common cause of complications of this procedure.[2] Bleeding complications may hinder the success of any surgery.[3] In recent years, several authors have reported on the perioperative administration of tranexamic acid (TXA) and its beneficial effect in reducing blood loss.[4]

TXA has been used to reduce blood loss and the need for transfusion in total hip and knee arthroplasty, with varying results.[5]

TXA is a synthetic antifibrinolytic drug whose effect results from the formation of a reversible complex of plasminogen and plasmin; it inhibits fibrinolysis and prevents lysis of the fibrin clot, and acts in the partial blockade of plasmin-induced platelet aggregation.[6] TXA can provide a hemostatic benefit in recurrent or excessive bleeding due to stabilization of fibrin structures and prevention of clot dissolution, especially when fibrin formation is impaired. Its effect on the preservation of the fibrin matrix can further enhance collagen synthesis and increase the elastic force of the tissue.[7]

TXA is quickly absorbed. Approximately 90% of an IV dose is excreted in the urine within 24 h; the plasma half-life is of approximately 2 h, and the therapeutic levels are maintained for 6–8 h. Its action preserves the clot and makes the hemostatic mechanism more efficient, reducing the intensity and risk of bleeding; it can be administered intravenously or topically.[8]

Currently, there is enough clinical evidence to recommend the use of TXA to reduce postoperative blood loss in total knee and hip arthroplasty. However, its optimal dose and regimens of administration are unknown.[9] At high concentrations, TXA can be a direct noncompetitive plasmin inhibitor. Peak plasma levels are achieved 5–15 min after intravenous administration.[7] Due to its low cost and minor side effects, research in different parts of the world has been conducted to assess TXA's effectiveness in controlling perioperative bleeding during major surgery.[6]

Bleeding reduction strategies have been used to decrease the need for transfusion of blood and blood products, due to the risks posed by these procedures. These risks include not only the transmission of viral and bacterial diseases, but also

Table 1 – Sample selection criteria.

Inclusion criteria
Primary total hip arthroplasty
Patients older than 18 years
Minimum accepted hemoglobin: 10 g/dL
Both genders
Exclusion criteria
Obesity with body mass index (BMI) > 40 kg m^{-2})
Patients younger than 18 years
Chronic kidney disease (creatinine clearance less than 60 mL/min m^2)
Bleeding disorders or thrombophilia
Trauma
Low platelet count (preoperative platelet count less than 150 000)
Chronic anemia (preoperative hemoglobin less than 10 g/dL)
Refusal to consent

the immunomodulation related to homologous transfusion, which has been of increasing concern especially considering the increase in the prevalence of infections in implanted prostheses, immunosuppression, and the previously evidenced association with the appearance of neoplasm in patients who receive this type of transfusion.[10]

Perioperative bleeding may require blood transfusions, which have their own complications and risks, and increase the costs of healthcare. Among other prevention methods, the effectiveness of treatment with TXA in reducing surgical blood loss has been demonstrated, especially in the immediate postoperative period.[11]

Thus, this study aimed to prove the efficacy of TXA in total hip arthroplasties when compared with a control group, to identify possible complications, and to establish a criterion for the ideal use of TXA.

Material and methods

The study included 42 patients submitted to primary THA, operated by the same team of surgeons, from February to November 2016. In this prospective and randomized study, patients were divided into three groups. Group 1 received TXA in a 15 mg/kg IV bolus dose 20 min before incision respecting a maximum dose of 2 g. Group 2 received TXA in a 15 mg/kg IV bolus dose 20 min before incision and an extra dose of 10 mg/kg using an infusion pump throughout the surgical procedure. Group 3, the control group, did not receive TXA. Pre- and postoperative hemoglobin levels were measured; blood loss was measured within 24 h after surgery using a Portovac drain. The mean peri- and postoperative bleeding, hemoglobin decrease, and need for blood transfusion were compared among the three groups. Table 1 presents the inclusion and exclusion criteria.

Statistical analysis

Results were expressed as means ± standard deviations (SD). One-way ANOVA was used for comparing the means, as this was a comparison of three independent groups. The normality assumptions were verified with the Shapiro–Wilk test, and variance homogeneity was assessed using the Levene test. Finally, the Tukey test was used to assess which differences were statistically significant. Results were considered to be statistically significant when $p < 0.05$. The statistical analyses were performed with IBM Statistics SPSS version 19.

Results

According to the preoperative inclusion criteria (Table 1), patients in group 1 (bolus), group 2 (bolus and pump), and group 3 (control) had mean hemoglobin levels above 10 g/dL: 14.33 mL/dL (95% CI: 13.05–15.55), 13.73 mL/dL (95% CI: 11.97–15.49), and 13.96 mL/dL (95% CI: 12.47–15.44; $p = 0.575$), respectively. Therefore, the groups were homogeneous regarding preoperative hemoglobin, with no statistically significant difference, which reduced the chance of interference due to discrepant preoperative hemoglobin values (Fig. 1).

Twenty-four hours after the primary THA procedure, a hemoglobin decrease was observed in the three groups, greatest in group 3 (Fig. 2). The mean hemoglobin level was 11.60 mL/dL (95% CI: 10.18–13.02) in group 1; 11.11 mL/dL (95% CI: 9.53–12.70) in group 2; and 10.37 mL/dL (95% CI: 8.67–12.07; $p = 0.130$) in group 3. These data demonstrate a statistically significant hemoglobin decrease in group 3 in relation to groups 1 and 2, demonstrating the beneficial effect of TXA regarding hemoglobin decrease in the first 24 h of the surgical procedure.

After 48 h of the primary THA procedure, a hemoglobin decrease was again observed in the three groups, and it was also greatest in group 3 (Fig. 2). The mean hemoglobin level was 10.92 mL/dL (95% CI: 9.53–12.30) in group 1; 10.89 mL/dL (95% CI: 9.44–12.33) in group 2; and 9.70 mL/dL (95% CI: 8.45–10.95; $p = 0.053$) in group 3. These data demonstrate a statistically significant hemoglobin decrease in group 3 in relation to groups 1 and 2, demonstrating the benefits of TXA regarding hemoglobin decrease in the first 48 h of the surgical procedure (Fig. 3).

The mean blood loss through the Portovac were 289.69 mL (95% CI: 146.90–432.48) in group 1; 250.00 mL (95% CI: 113.73–386.27) in group 2; and 437.92 mL (95% CI: 218.40–657.44; $p = 0.017$) in group 3.

Group 3 presented statistically significant higher blood loss through the Portovac drain when compared to group 1 (bolus) and group 2 (bolus and pump), as shown in Fig. 4. Therefore, it can be concluded that there was a significant increase in the volume of bleeding measured in the Portovac drains of patients in group 3 compared to groups 1 and 2, a statistically significant value. It again suggests a beneficial effect of TXA regarding decreased bleeding. No statistically significant differences were observed between groups 1 and 2.

Discussion

Studies evaluating TXA in orthopedic surgery demonstrated its effectiveness and safety when administered intravenously or intra-articularly.[11] In their studies, Yamasaki et al.[12] assessed the effects of TXA in 40 patients undergoing uncemented THA. Twenty patients were administered 1000 mg of TXA intravenously 5 min prior to the start of the operation. The other 20 patients served as controls and were operated on without TXA. The perioperative blood loss was similar between groups. In turn, postoperative blood loss in the TXA

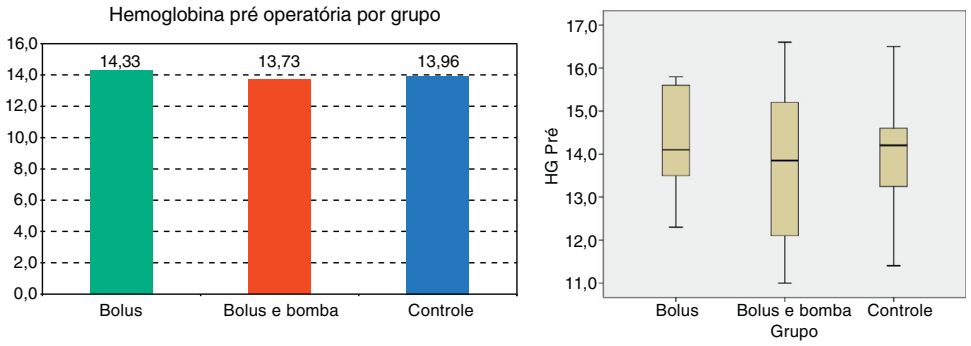

Fig. 1 – Comparison of preoperative hemoglobin by group.

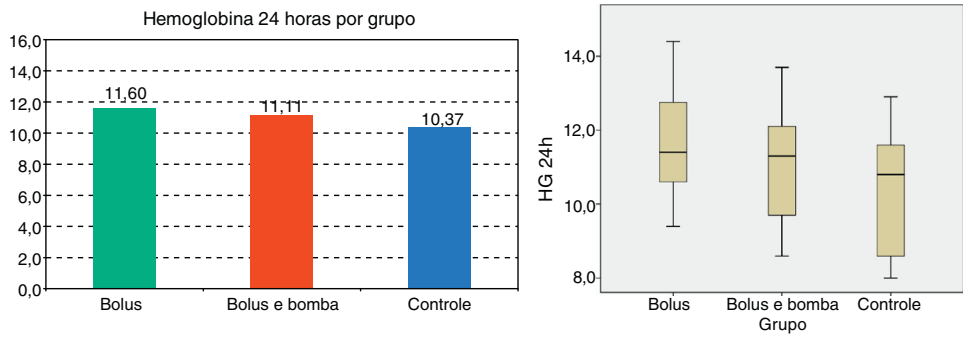

Fig. 2 – Comparison of 24-h hemoglobin by group.

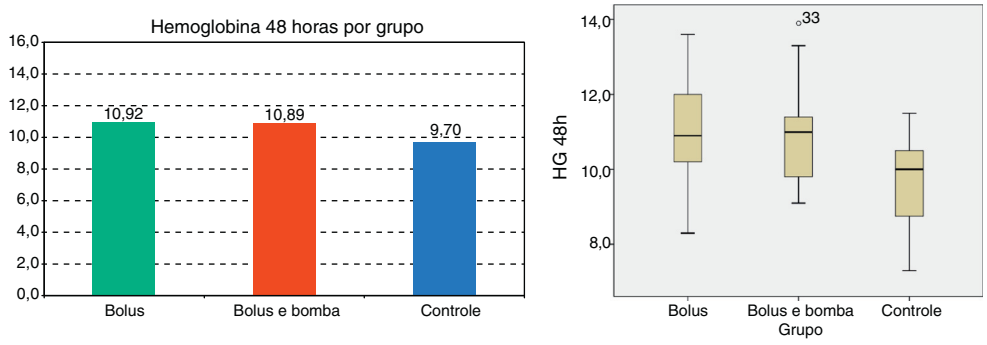

Fig. 3 – Comparison of 48-h hemoglobin by group.

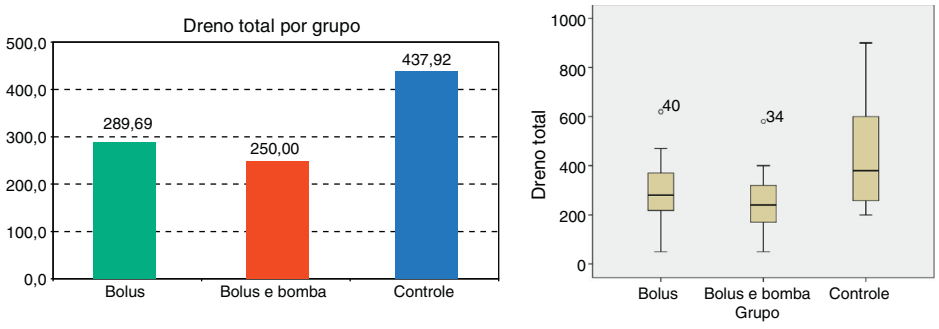

Fig. 4 – Total drainage by group.

group was significantly lower than that of the control group at 2, 4, 6, 8, 10, and 12 h. Regarding the time of alterations related to postoperative blood loss, a significant reduction was observed in the first 2 h after surgery in the TXA group ($p < 0.001$). After 2 h, no significant differences were observed between the TXA group and the control group. Preoperative administration of TXA reduced postoperative blood loss at up to 12 h, as well as the total bleeding in cemented THA, due to the reduction of blood loss during the first 2 h after surgery.

Zhou et al.[13] have shown that TXA reduced blood loss and transfusion requirements in patients undergoing THA. The use of TXA significantly reduced mean total blood loss on a mean volume of 305.27 mL (95% CI: −397.66 to −212.89; $p < 0.001$); being 86.33 mL mean intraoperative blood loss (95% CI: −152.29 to −20.37; $p = 0.01$); 176.79 mL mean postoperative blood (95% CI: −236.78 to −116.39; $p < 0.001$); and 152.70 mL mean occult blood loss (95% CI: −187.98 to −117.42; $p < 0.001$). This resulted in a significant reduction in the proportion of patients who needed blood transfusions (odds ratio 0.28; 95% CI: 0.19–0.42; $p < 0.001$). There was no significant difference in the occurrence of deep venous thrombosis, pulmonary embolism, or other complications between study groups, or the cost or duration of hospitalization.

Rocha et al.[6] reported a protocol in which TXA was used at a loading dose of 10 mg/kg body weight, administered during the 30 min prior to skin incision. The maximum dose of 2 g of drug was observed. After the incision was made, continuous infusion of TXA was maintained at a rate of 30 mg/kg/h until the skin was sutured. These authors also reported that this protocol has been safely used in other centers.

In a randomized controlled trial comparing the effect of TXA and fibrin spray on blood loss in cemented THA, McConnell et al.[14] administered a single 10 mg/kg bolus dose of intravenous TXA during anesthesia induction. According to these authors, the manufacturer did not specify a recommended dose for this surgery, therefore the dose and time were chosen by them, based on previous studies, which have demonstrated the effectiveness of a bolus dose of 10 mg/kg during induction in hip arthroplasty. A randomized, double-blinded study assessed the effect of TXA on blood loss and blood transfusions in 40 primary THAs. TXA at a dose of 10 mg/kg body weight, or placebo, were administered intravenously shortly before surgery. Blood loss during operation and postoperative drainage were measured, as well as serum hemoglobin concentrations. An ultrasound scan was performed one week postoperatively to estimate blood loss due to remaining hematomas. Total blood loss (surgery + drainage) was 0.76 (95% CI: 0.63–0.89) in the TXA group, and 1.0 (95% CI: 0.81–1.2) in the placebo group ($p = 0.03$). The number of blood transfusions on the day of surgery was 2 *vs.* 10 ($p = 0.07$) and total number of blood transfusions during the hospitalization period was 5 *vs.* 13 ($p = 0.2$). One patient in each group had pulmonary embolism.[15]

In a prospective, randomized, double-blinded study, Husted et al.[16] studied 40 patients scheduled for primary THA to determine the effect of TXA on perioperative and postoperative blood loss and on the number of blood transfusions required. These patients were randomized to receive TXA (10 mg/kg administered as an intravenous bolus injection, followed by a continuous infusion of 1 mg/kg/h for 10 h) or placebo (20 mL saline solution, intravenously) 15 min before incision. Peri- and postoperative blood loss (recorded at drain removal, 24 h after the operation) were recorded, as well as the number of blood transfusions. Patients who received TXA had a mean perioperative blood loss of 480 mL *vs.* 622 mL in patients receiving placebo ($p = 0.3$); mean postoperative blood loss of 334 mL *vs.* 609 mL ($p = 0.001$); mean total blood loss of 814 mL *vs.* 1231 mL ($p = 0.001$), and a total need for blood transfusions of 4 *vs.* 25 ($p = 0.04$). No patient in any group had deep venous thrombosis, pulmonary embolism, or prolonged wound drainage.

In elective surgery, TXA reduces the need for blood transfusion by approximately 30%, without affecting mortality or increasing postoperative complications. In trauma, TXA was recently associated with a reduction in the mortality rate in a large number of trauma patients with bleeding.[17] TXA significantly decreases postoperative blood loss in a remarkable difference (50–460 mL). Total perioperative blood loss was reduced by 440 mL on average.[18] Drugs such as TXA and aminocaproic acid have been used in large elective surgeries to prevent fibrinolysis by reducing the number of blood transfusions. However, although their use is very attractive for the coagulopathy of trauma, there are currently no data from studies in humans that support its routine application in trauma.[19] Intravenous TXA can reduce blood loss[13,20] and the need for transfusion in patients undergoing THA, without increasing the risk of complications.[13] There is little data regarding the adverse effects of this drug. It rarely causes hypotension and retinal alteration. Its prolonged systemic use increases the risk of thromboembolic phenomena; it is contraindicated in acute thrombopathies and should be used with caution in patients with a known tendency for thrombosis.[21] Studies on the use of TXA showed interesting results, but its benefits in THA have not been well established.[22]

Conclusion

The findings of the present study demonstrated that the use of intravenous TXA in THA reduced the rates of postoperative bleeding and, consequently, significant decreased in serum hemoglobin was observed in groups 1 (bolus) and 2 (bolus and infusion pump) when compared to group 3 (control: did not receive TXA). Therefore, there was a reduction in the need for blood transfusion, which was required for two patients in the control group. Patients in groups 1 and 2 did not require blood transfusion. Regarding the different administration protocols, the use of bolus and bolus added to infusion pump methods have shown a very similar influence on serum hemoglobin and the amount of blood loss through Portovac drains; the differences were not statistically significant.

No statistically significant differences were observed regarding hemoglobin decrease and blood loss through the drains between patients in groups 1 and 2. Therefore, it is suggested that the use of a TXA administration protocol at a dose of 15 mg/kg in bolus 30 min prior to skin incision in patients undergoing THA may be more advantageous, as the dose is lower, consequently decreasing the risks of side effects and reducing the costs and complexity of administration.

No thromboembolic effects were observed in the patients of this study.

Conflicts of interest

The authors declare no conflicts of interest.

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