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RESEARCH ARTICLE

EFFICACY AND SAFETY OF TRANEXAMIC ACID FOR CONTROLLING BLEEDING DURING SURGICAL TREATMENT OF INTERTROCHANTERIC FRAGILITY FRACTUR

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ABSTRACT

Background: Intertrochanteric fragility fracture (IFF) treated with proximal femoral nail anti-rotation (PFNA) is associated with significant hidden blood loss and high blood transfusion rate. The purpose of the present study was to evaluate the efficacy and safety of tranexamic acid (TXA) in reducing blood loss in these patients. **Materials and Methods:** Consecutive eligible patients were recruited and randomly assigned to a TXA group or a control group. The TXA group received 15 mg/kg body weight of TXA intravenously 15 min before incision and the same dose 3 h later. The control group received 100 mL of saline intravenously 15 min before incision. The efficacy outcomes included the total perioperative blood loss, postoperative transfusion rate, postoperative hemoglobin level, and length of the hospital stay. The safety outcomes were the incidence of thrombotic events and the mortality rate within 6 weeks after surgery. **Results:** We had 44 patients in the TXA group and 46 patients in the control group for the final analysis. The TXA group had significantly lower total perioperative blood loss than the control group (384.5 ± 366.3 mL vs. 566.2 ± 361.5 mL; P <0.020). Postoperative transfusion rate was 15.9% in the TXA group versus 36.9% in the control group (P = 0.024). **Conclusion:** Intravenous TXA is effective in reducing total perioperative blood loss and rate in IFF treated with PFNA. No increased risk of thrombotic events was observed with the use of TXA; however, this study was underpowered for detecting this outcome. Further research is necessary before TXA can be recommended for high-risk patients.

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INTRODUCTION

Proximal femoral nail anti-rotation (PFNA) is widely used for treating intertrochanteric fragility fractures (IFF), because of its many advantages: It is minimally invasive, it is associated with relatively lower amount of intraoperative blood loss, and it provides stable fixation with few complications. However, the total blood loss is much greater than that observed intraoperatively. The high rate of postoperative anemia and blood transfusion indicate that there had been much-hidden blood loss, which is reported to be as much as 673.2 ± 97.5 mL1 and 734.2 ± 455.7 mL.2 Unfortunately, few studies have focused on investigating the perioperative hidden blood loss in intertrochanteric fractures. So far, the reasons and mechanism of hidden blood loss in hip fractures are not very clear. Foss *et al*.3 believed this hidden blood loss may came from continuous bleeding after the operation, gastrointestinal tract, and initial trauma bleeding, and the use of anticoagulant drugs could also aggravate postoperative bleeding. Millar *et al*. 4 suggested that the hidden hemorrhage was related to the opening of the medullary cavity. Smith *et al*.5 and Bao *et al*.6 considered that reaming of intramedullary could lead to the release of free fatty acids and the abnormal opening of the capillary bed that caused the blood flow into the tissue space. Elderly patients have poor tolerance of acute anemia, and literature reports show that up to 41.6% of patients in this age group will require allogeneic blood transfusion to replace the lost blood.2 Nevertheless, allogeneic blood transfusion is associated with adverse events such as allergic reactions, transmission of infectious diseases, hemolytic reaction, and transfusion-related acute lung injury. Therefore, effective blood-conservation interventions are needed. A variety of methods are used in orthopaedic surgery to reduce blood loss, including the application of tourniquets, autologous blood transfusion, controlled hypotension, intraoperative blood salvage, navigation, and minimally invasive surgery. However, these methods are not easily and effectively implemented in IFF treated with PFNA. Antifibrinolytic drugs have been used to reduce blood loss in surgery, but it is not recommended in hip fracture surgery because the hip fracture is associated with high incidence of deep venous thrombosis (DVT). In fact, anticoagulants are routinely used to prevent DVT after hip fracture surgery, but this may result in further increase in the blood loss. This is a conundrum that needs further research. In recent years, many studies have demonstrated that tranexamic acid (TXA) can effectively reduce blood loss and transfusion

rate in hip and knee replacement surgery, without increasing the incidence of thrombotic events.9-11 However, few studies have investigated the efficacy and safety of TXA in IFF treated with PFNA. Zufferey *et al*.12 published a randomized controlled trial (RCT) in 2010 in which they reported that TXA reduced the need for erythrocyte transfusion in hip fracture surgery, but that there was a trend for increased risk of vascular events with the use of TXA. Thus, no definite conclusions could be drawn from the trial regarding the clinical benefit-risk ratio of TXA. In the present study, we aimed to determine (1) whether intravenous TXA could significantly reduce perioperative blood loss and transfusion rate in IFF undergoing PFNA fixation surgery and (2) whether there was any increase in the risk of thrombotic events.

MATERIALS AND METHODS

Recruitment was from September 2017 to January 2019. All participants or their relatives provided written informed consent before randomization in the trial.

Inclusion and exclusion criteria: Patients were eligible for inclusion if they (1) had intertrochanteric fracture (extracapsular fractures of AO/OTA types 31-A1 to 31-A3) treated with PFNA, (2) closed fracture with low-energy damage, and (3) age ≥60 years. Patients were excluded if (1) preoperative examination revealed DVT; (2) they had any contraindication for anticoagulation therapy; (3) they had a pathological fracture; (4) they had one of the following diseases in the preceding year: myocardial infarction, cerebral infarction, coronary syndrome, DVT, or pulmonary embolism; (5) the duration from injury to operation was >3 weeks; (6) they had allergy to TXA; (7) patients who had adverse drug reactions when using TXA and stopped the medication; (8) they had multiple fractures, with the other fracture also needing surgical treatment; (9) preoperative hemoglobin (Hb) was <8 g/dL; (10) closed reduction failed, and therefore open reduction was performed; and (11) there was any change in the fixation method or if, intraoperatively, the decision was made to perform arthroplasty. Patients who were on anticoagulant therapy were not excluded; they were asked to stop anticoagulation therapy 5 days before the operation.

Randomization and blinding: Randomization was performed using a computer-generated random number table and sealed envelopes for the treatment allotment. The patient and the investigator were blinded to the group allocation. An orthopaedic resident was responsible for the allocation of patients to the different groups. On the day of surgery, the anesthesiologist received the sealed envelope from the orthopaedic resident and administered the allotted drug. TXA group patients received a dose of 15 mg/kg body weight of TXA intravenously 15 min before incision and the same dose again 3 h later. Control group patients received 100 mL of saline intravenously 15 min before incision.

Sample size: Sample size calculation was based on a previous report (a meta-analysis) that found that TXA reduces blood loss in patients undergoing total hip arthroplasty by a mean amount of 305 mL.9 Because the amount of blood loss in IFF treated with PFNA is less than that in total hip arthroplasty, the efficacy of TXA in the former is likely to be less obvious. Using a delta value of 200 mL and an overall standard deviation of 280 mL, we estimated that at least 41 cases would be needed in each group to detect a difference of this magnitude with $\beta = 0.10$ and $\alpha = 0.05$. We, therefore, enrolled 50 patients in each group.

Outcome measures: The primary efficacy outcome was the total perioperative blood loss. The total blood loss was calculated based on the hematocrits (Hcts) level and the estimated blood volume. The latter was determined according to gender, body mass, and height. Hidden blood loss can be calculated from the total blood loss and obvious intraoperative blood loss. The total perioperative blood loss was calculated using the following formulas:

- PBV = height (m)3 × 0.3669 + weight (kg) × 0.03219 + 0.6041 (for men), and
- PBV = height (m)3 × 0.3561 + weight (kg) × 0.03308 + 0.1833 (for women)13
- EBV = PBV × (Hctpre-op − Hctpost-op)/Hctav

Total perioperative blood loss (mL) = EBV + blood transfused, where PBV = patient's blood volume; EBV = estimated blood loss; Hctpre-op = preoperative Hct; Hctpost-op = postoperative Hct; and Hctav = average of the preoperative and postoperative Hct. Hb and Hct were measured 1 day before surgery and then again on postoperative day 3. These values were used to calculate the total perioperative blood loss. In patients receiving blood transfusion, 1 unit of concentrated red blood cells (CRBCs) was considered equivalent to 200 mL whole blood. Intraoperative blood loss was evaluated by measuring suction loss plus the weight of loss in gauze. The secondary efficacy outcomes were postoperative transfusion rate, postoperative Hb, and duration of hospital stay. The requirement for allogeneic CRBC in each group was recorded. The American Academy of Orthopaedic Surgeons recommends postoperative blood transfusion in hip fracture patients when Hb is <8 g/dL, even if symptoms are not present.15 Accordingly, in the present study, blood transfusion was administered (1) if Hb was <8 g/dL or (2) if Hb was ≥8 g/dL, but there were signs of excess blood loss such as tachycardia, tachypnea, or hemodynamic instability.

The primary safety outcome was the occurrence of thrombotic events within 6 weeks after operation; these included lower limb DVT, pulmonary embolism, myocardial infarction, acute coronary syndrome, cerebral infarction, and extremity ischemic necrosis. All patients underwent Dopple ultrasonography of both lower limbs before operation as well as at discharge. An orthopaedic specialist was responsible for the followup. Patients were encouraged to visit the hospital within 1 month after discharge. Patients who did not visit the hospital for followup were contacted over the telephone to obtain information on lower limb swelling or other complications. The secondary safety outcomes included mortality rate within 6 weeks after operation and any adverse events related to TXA.

Operative procedure: All operations were performed by two experienced orthopaedic surgeons. Prophylactic antibiotics were administered 30～60 min before operation. Either spinal or general anesthesia was administered, and the patients were positioned on the fracture traction table. Closed reduction was performed under C-arm fluoroscopy. PFNA was inserted using the minimally invasive technique. After closed reduction, an approximately 5 cm longitudinal skin incision was made proximal to the femoral greater trochanter. The tip of the greater trochanter was exposed by incision of the fascia and the

gluteus medius. A guide needle was drilled into the femoral medullary canal from the lateral aspect of the greater trochanter, and the intramedullary nail was inserted through the guide needle. The blade was located in the lower half of the femoral head and neck in the anteroposterior view and centrally in the lateral view; the tip was inserted 5～10 mm into subchondral bone. The distal locking screw was inserted under an aiming device and was statically locked. No postoperative drainage was performed.

Postoperative management: Antibiotic prophylaxis was administered routinely for 48 h postoperatively. The volume of fluid transfusion was determined by the surgeon in charge according to the patient's blood pressure and amount of oral intake. Low-molecular-weight heparin was administered routinely every 24 h postoperatively for 2 weeks to prevent thromboembolism. Active functional exercises were encouraged from postoperative day 1. The continuous passive motion was started in all patients on the second postoperative day. Partial weight-bearing with a walker was started 1-week postoperatively in stable fractures treated with satisfactory reduction and internal fixation; in those with unstable fractures, this was started 2–3 weeks postoperatively.

Statistical analysis: Continuous variables were reported as mean ± standard deviation or median. Categorical variables were reported as frequency and percentage. The normality of distribution of continuous variables was tested by the Kolmogorov–Smirnov test. The independent-samples t-test was used for normally distributed continuous variables and the Mann–Whitney U-test for non-normally distributed variables. Categorical variables were tested by the Pearson Chi-square test. Two-tailed $P < 0.05$ was considered to be statistically significant.

RESULTS

A total of 100 eligible patients were enrolled in the study at our hospital between September 15, 2017, and January 10, 2019. Of these, 50 were randomized to the TXA group and 50 to the control group. After excluding six patients in whom the treatment plan was changed to open reduction and four patients with incomplete postoperative test results, we had 44 patients in the TXA group and 46 patients in the control group for the final analysis [Figure 1]. No patients were lost to follow up. There were no significant differences in the baseline characteristics between the two groups [Table 1]. 14Surgical time was 60.4 ± 10.3 min in the TXA group versus 62.5 ± 9.1 min in the control group ($P = 0.305$). Total perioperative blood loss was significantly lower in the TXA group than in the control group (384.5 ± 366.3 mL vs. 566.2 ± 361.5 mL; $P < 0.020$). Postoperative CRBC transfusion rate was significantly lower in the TXA group than in the control group (15.9% vs. 36.9%; $P = 0.024$). The length ofmhospital stay was significantly shorter in the TXA group than in the control group [16.8 ± 2.9 days vs. 18.6 ± 3.6 days; $P = 0.008$, Table 2]. Each group had one patient with postoperative DVT.

DISCUSSION

TXA has been widely used for decades for reducing blood loss in cardiac surgery, liver surgery, trauma, and nonsurgical diseases.16 In recent years, TXA has been shown to be safe and effective for reducing blood loss during total joint arthroplasty. 17 However, few studies have focused on the use of TXA in IFF treated with PFNA. In the present study, we found that administrating two doses of TXA in IFF undergoing PFNA significantly decreased the total perioperative blood loss and transfusion rate without increasing the incidence of thrombotic events. Surgeons usually do not use hemostatic drugs when they treat IFF with PFNA, because it is a minimally invasive procedure with little obvious blood loss. Tang *et al*.18reported a median blood loss of only 75 mL during operation. However, the surgery is associated with massive hidden blood loss that is followed by mild or severe acute anemia, especially in elderly patients, and these patients often need allogeneic blood transfusion postoperatively.

Therefore, it is necessary to identify methods that can reduce blood loss in these patients. The current study showed that the total perioperative blood loss was significantly decreased with the use of TXA (384.5 ± 366.3 mL with TXA vs. 566.2 ± 361.5 mL without TXA). Two doses of TXA prevented about 180 mL blood loss per patient in the treatment group. Although this may not seem a large amount, it is a crucial volume in elderly patients, and preventing this blood loss can significantly reduce the need for transfusion. In the present study, where the threshold for transfusion was Hb <8 g/dL, blood transfusion was needed in only 15.9% of patients in the TXA group versus 36.9% in the control group. This difference of 21.0% means that the number needed to treat is about 5, i.e., five patients need to be treated with TXA to prevent one blood transfusion. These results are in accordance with the findings of an RCT performed in 2015, which showed that in IFF surgery, the need for blood transfusion was significantly reduced in patients receiving TXA; in that study, 18% patients in the intervention group versus 42% in the control group required blood transfusion.19 Vijay *et al*.20 and Sadeghi and Mehr-Aein21 have also reported that TXA significantly reduced perioperative blood loss and transfusion rate in patients undergoing hip fracture surgeries.

A recent RCT22 comparing TXA with placebo found that, in patients undergoing surgery for unstable trochanteric fracture, blood loss was 570.8 mL lower in the TXA group than in the placebo group ($P = 0.029$). However, one earlier study has reported a contrary finding: an RCT, performed in 2010, found that there was no significant difference in blood transfusion rates between TXA and placebo groups after hip fracture surgery (42% vs. 60%; $P = 0.06$).12 Farrow *et al*.23 performed a meta-analysis in 2016 of the use of TXA in hip fracture surgery and demonstrated that intravenous TXA resulted in a 46% risk reduction in the need for blood transfusion compared to the placebo/control patients. TXA therapy can be beneficial in IFF surgery with PFNA. Elderly patients often have coexisting cardio-cerebral-vascular diseases and are particularly vulnerable to hemodynamic fluctuations. TXA can be protective in these patients as it helps maintain hemodynamic stability by reducing blood loss during operation. In addition, Jimenez *et al*.24 have reported that TXA possibly attenuates the inflammatory response and its adverse effects on hemodynamic stability. Secondary anemia is common in IFF patients in the perioperative period. Allogeneic blood transfusion can improve postoperative anemia but may also cause adverse events. TXA, by reducing the requirement for blood transfusion, thus also reduces the risk of transfusion-related adverse events. The use of TXA in IFF surgery also provides economic benefits. In China, the cost of 2 g of TXA is about RMB 60, which is significantly lower than the cost of

1 unit of CRBC (about RMB 260). The use of TXA improves postoperative Hb values, which leads to quicker recovery and shorter hospital stay, thereby further decreasing treatment-related costs. Recently published studies have shown that TXA is cost effective25,26 in total hip and knee arthroplasty. Gillette *et al*.25 reported that the total costs were significantly lower for patients who received TXA, with an estimated mean hospital total cost saving of US $879 per patient. The fact that TXA significantly reduces the requirement for blood transfusion may provide a method for resolving the problem of blood scarcity. With the population aging, the incidence of hip fracture has rapidly increased in China. Most patients require surgery, and up to 41.6% may need blood transfusion.2 In this scenario, clinicians are often faced with the problem of blood scarcity.

In the present study, we have demonstrated that 1.5 units of CRBC can be saved for every five patients treated with TXA, which means that a considerable amount of allogeneic blood transfusions could be avoided with the wide use of TXA in hospitals. Despite the evident benefits from the administration of TXA in IFF surgery, there are still some concerns about the incidence of thrombotic events after TXA use. In our study, no statistically significant increase in thrombotic events was observed in patients treated with TXA. However, Zufferey *et al*.12 have reported that using TXA in hip fracture surgery increased the risk of vascular events compared with placebo. Many recent studies have demonstrated that administration of TXA in total joint arthroplasty surgery does not increase the risk of DVT.27-29 In 2012, Whiting *et al*. 30 performed a retrospective review of 1131 primary total joint arthroplasties in 1002 patients with the American Society of Anesthesio logists Score III or IV. The aim was to investigate how the use of TXA affected the incidence of thromboembolic events in patients with severe medical comorbidities. The authors found no significant difference in the incidence of symptomatic thromboembolic events within 30 days of surgery between patients who received TXA and those who did not (2.5% vs. 2.6%; P = 0.97). In patients with high-risk factors for thromboembolic disease, TXA was not associated with significant increase in the incidence of symptomatic thromboembolic events (6.7% in patients receiving TXA vs. 4.3% in patients not receiving TXA; P = 0.27).

Roberts *et al*.,31 after stratified analysis of data from an international multicenter RCT (the CRASH-2 trial), reported that TXA-treated patients had significant reduction in the risk of arterial thrombotic events (Odds ratio 0.58, 95% confidence interval [CI]: 0.40–0.83; P = 0.003), but not in the risk of venous thrombotic events (Odds ratio 0.83, 95% CI: 0.59–1.17; P = 0.295). Our study has several limitations. First, the volume of intravenous fluids administered after operation was not controlled, and this may have confounded the total perioperative blood loss calculation. Second, the study was statistically underpowered to detect the difference in incidence of thrombotic events between the two groups. A much larger sample would be needed to detect differences in the incidence of thrombotic events as such events are relatively rare in these patients who receive comprehensive measures for prevention of thrombosis postoperatively. Third, a selection bias may exist due to failure to control for certain factors (e.g., the proportion of patients with previous comorbidities or anticoagulant therapy) and to differences in the delivered standard of care (preoperative time to operation, anesthesia, and so on).

Conclusion

Intravenous TXA can effectively reduce the total operative blood loss and the need for transfusion in IFF treated with PFNA. No increased risk of thrombotic events was observed in our sample with the use of TXA; however, the study was underpowered for detecting this outcome. Further research is necessary before TXA can be recommended for high-risk patients.

Ethical approval and consent to participate: Informed consent was obtained from all individual participants included in the study.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest: There are no conflicts of interest.

REFERENCES

Wei, J., Wang, J., Gao, M. and Wang, M. 2015. Analysis of perioperative blood loss in treatment of senile hip fractures. *Chin J Orthop Trauma*., 2015;17:104-7.

Hou, GJ., Zhou, F., Zhang, ZS., Ji, HQ. and Tian, Y. 2013. Analysis of the blood loss in perioperative period of femoral intertrochanteric fractures in old patients treated with different internal fixations. Beijing Da Xue Xue Bao Yi Xue Ban 45:738-41.

Foss, NB. and Kehlet, H. 2006. Hidden blood loss after surgery for hip fracture. *J Bone Joint Surg Br.,* 88:1053-9.

Millar, NL., Deakin, AH., Millar, LL. and Kinnimonth, AW. 2011. Picard F. Blood loss following total knee replacement in the morbidly obese: Effects of computer navigation. Knee, 18:108-12.

Smith, GH., Tsang, J., Molyneux, SG. and White, TO. 2011. The hidden blood loss after hip fracture. Injury, 42:133-5.

Bao, N., Zhou, L., Cong, Y., Guo, T., Fan, W., Chang, Z., *et al*., 2013. Free fatty acids are responsible for the hidden blood loss in total hip and knee arthroplasty. *Med Hypotheses,* 81:104-7.

Piovella, F., Wang, CJ., Lu, H., Lee, K., Lee, LH., Lee, WC., *et al*., 2005. Deep-vein thrombosis rates after major orthopedic surgery in Asia. An epidemiological study based on postoperative screening with centrally adjudicated bilateral venography. *J Thromb Haemost.,* 3:2664-70.

Lee, SY., Ro du, H., Chung, CY., Lee, KM., Kwon, SS., Sung, KH., *et al*., 2015. Incidence of deep vein thrombosis after major lower limb orthopedic surgery: Analysis of a nationwide claim registry. *Yonsei Med J.,* 56:139-45.

Zhou, XD., Tao, LJ., Li, J. and Wu, LD. 2013. Do we really need tranexamic acid in total hip arthroplasty? A meta-analysis of nineteen randomized controlled trials. *Arch Orthop Trauma Surg.*, 133:1017-27.

Wu, Q., Zhang, HA., Liu, SL., Meng, T., Zhou, X., Wang, P., *et al*., 2015. Is tranexamic acid clinically effective and safe to prevent blood loss in total knee arthroplasty? A meta-

analysis of 34 randomized controlled trials. *Eur J Orthop Surg Traumatol.,* 25:525-41.

Sukeik, M., Alshryda, S., Haddad, FS. and Mason, JM. 2011. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. *J Bone Joint Surg Br.,* 93:39-46.

Zufferey, PJ., Miquet, M., Quenet, S., Martin, P., Adam, P., Albaladejo, P., *et al*., 2010. Tranexamic acid in hip fracture surgery: A randomized controlled trial. *Br J Anaesth.,* 104:23-30.

Nadler, SB., Hidalgo, JH. and Bloch, T. 1962. Prediction of blood volume in normal human adults. *Surgery,* 51:224-32.

Gross, JB. 1983. Estimating allowable blood loss: Corrected for dilution. *Anesthesiology*, 58:277-80.

Roberts, KC., Brox, WT., Jevsevar, DS. and Sevarino, K. 2015. Management of hip fractures in the elderly. *J Am Acad Orthop Surg*., 23:131-7.

Ng, W., Jerath, A. and Wąsowicz, M. 2015. Tranexamic acid: A clinical review. *Anaesthesiol Intensive Ther.,* 47:339-50.

Jennings, JD., Solarz, MK. and Haydel, C. 2016. Application of tranexamic acid in trauma and orthopedic surgery. *Orthop Clin North Am.,* 47:137-43.

Tang, P., Hu, F., Shen, J., Zhang, L. and Zhang, L. 2012. Proximal femoral nail antirotation versus hemiarthro plasty: A study for the treatment of intertro chanteric fractures. *Injury*, 43:876-81.

Mohib, Y., Rashid, RH., Ali, M., Zubairi, AJ. and Umer, M. 2015. Does tranexamic acid reduce blood transfusion following surgery for inter-trochanteric fracture? A randomized control trial. *J Pak Med Assoc.,* 65:S17-20.

Vijay, BS., Bedi, V., Mitra, S. and Das, B. 2013. Role of tranexamic acid in reducing postoperative blood loss and transfusion requirement in patients undergoing hip and femoral surgeries. *Saudi J Anaesth.,* 7:29-32.

Sadeghi, M. and Mehr-Aein, A. 2007. Does a single bolus dose of tranexamic acid reduce blood loss and transfusion requirements during hip fracture surgery? A prospective randomized double blind study in 67 patients. *Acta Med Iran.,* 45:437-42.

Tengberg, PT., Foss, NB., Palm, H., Kallemose, T. and Troelsen, A. 2016. Tranexamic acid reduces blood loss in patients with extracapsular fractures of the hip: Results of a randomised controlled trial. *Bone Joint J.,* 98-B: 747-53.

Farrow, LS., Smith, TO., Ashcroft, GP. and Myint, PK. 2016. A systematic review of tranexamic acid in hip fracture surgery. *Br J Clin, Pharmacol.,* 82:1458-70.

Jimenez, JJ., Iribarren, JL., Lorente, L., Rodriguez, JM., Hernandez, D., Nassar, I., *et al*., 2007. Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: A case control study followed by a randomized double-blind controlled trial. *Crit Care.,* 11:R117.

Gillette, BP., Maradit Kremers, H., Duncan, CM., Smith, HM., Trousdale, RT., Pagnano, MW., *et al*., 2013. Economic impact of tranexamic acid in healthy patients undergoing primary total hip and knee arthroplasty. *J Arthroplasty.,* 28:137-9.

Irisson, E., Hémon, Y., Pauly, V., Parratte, S., Argenson, JN., Kerbaul, F., *et al*., 2012. Tranexamic acid reduces blood loss and financial cost in primary total hip and knee replacement surgery. *Orthop Traumatol Surg Res.,* 98:477-83.

Gillette, BP., DeSimone, LJ., Trousdale, RT., Pagnano, MW. and Sierra, RJ. 2013. Low risk of thromboembolic complications with tranexamic acid after primary total hip and knee arthroplasty. *Clin Orthop Relat Res.,* 471:150-4.

Wu, YG., Zeng, Y., Yang, TM., Si, HB., Cao, F., Shen, B., *et al*., 2016. The efficacy and safety of combination of intravenous and topical tranexamic acid in revision hip arthroplasty: A Randomized, controlled trial. *J Arthroplasty,* 31:2548-53.

Formby, PM., Pickett, AM., Van Blarcum, GS., Mack, AW. and Newman, MT. 2015. The use of intravenous tranexamic acid in patients undergoing total hip or knee arthroplasty: A retrospective analysis at a single military institution. *Mil Med.,* 180:1087-90.

Whiting, DR., Gillette, BP., Duncan, C., Smith, H., Pagnano, MW., Sierra, RJ., *et al*., 2014. Preliminary results suggest tranexamic acid is safe and effective in arthroplasty patients with severe comorbidities. *Clin Orthop Relat Res.,* 472:66-72.

Roberts, I., Perel, P., Prieto-Merino, D., Shakur, H., Coats, T., Hunt, BJ., *et al*., Effect of tranexamic acid on mortality in patient with traumatic bleeding: Prespecified analysis of data from.

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