ORIGINAL ARTICLE

Intra-operative local plus systemic tranexamic acid significantly decreases post-operative bleeding and the need for allogeneic blood transfusion in total knee arthroplasty

Lidia De Falco[1,2], Elisa Troiano[1,2], Martina Cesari[1,2], Pietro Aiuto[1,2], Giacomo Peri[1,2], Nicolò Nuvoli[1,2], Mattia Fortina[1,2], Nicola Mondanelli[1,2], Stefano Giannotti[1,2]

[1]Section of Orthopaedics and Traumatology, Department of Medicine Surgery and Neurosciences, University of Siena, [2]Section of Orthopaedics and Traumatology, Azienda Ospedaliera Universitaria Senese; Siena, Italy

ABSTRACT

Aim To evaluate the efficacy of systemic plus local tranexamic acid (TXA) in reducing post-operative bleeding, haemoglobin loss and the need for allogeneic blood transfusion (ABT) in total knee arthroplasty (TKA).

Methods All patients undergoing TKA between January 2017 and September 2019 were retrospectively evaluated. Exclusion criteria were cardiovascular comorbidities, diabetes and the assumption of any anticoagulant/antiaggregant therapy in the pre-operative period. All patients received the same prosthesis with the same surgical technique and were operated on by the same surgeon. Twenty patients were found (group A) that received intra-operative TXA (20 mg/kg intravenous 10 minutes before deflating tourniquet and 1g intra-articular after capsular suture). A control group of 26 patients not receiving TXA was matched for demographics (group B).

Results Two (10%) patients in group A and 16 (61.5%) in group B needed ABT in the post-operative period (p=0.0004). Each patient in group A received 2 red blood cells (RBCs) units, while in group B 2 patients received one RBCs unit and one patient 4 RBCs units, for a total of 4 and 32 RBCs units in group A and B, respectively (p=0.0006). The minimum haemoglobin level was observed at 48 hours post-operatively in both groups: mean decrease was 3.54 and 4.64 g/dL in group A and B, respectively (p=0.0126).

Conclusion The association of systemic and local TXA administration seems to significantly reduce post-operative bleeding and the need for RBCs transfusions after TKA in patients not assuming any anticoagulant / antiaggregant therapy and without cardiovascular and diabetic morbidities.

Key words: bleeding, haemoglobin, orthopaedic surgery, post-operative anaemia, red blood cells

Corresponding author:
Nicola Mondanelli
Section of Orthopaedics, Department of Medicine, Surgery and Neurosciences, University of Siena
Viale Mario Bracci 16, 53100 Siena, Italy
E-mail: nicola.mondanelli@unisi.it
Phone: +39 0577 585 675;
Fax +39 0577 233 400;
De Falco Lidia ORCID ID: https://orcid.org/0000-0003-3756-9033

Original submission:
02 December 2020;
Accepted:
11 December 2020
doi: 10.17392/1327-21

INTRODUCTION

Total knee arthroplasty (TKA) generally involves significant post-operative anaemia, because of the continuous bleeding from the cut bone surfaces (the femur more than the tibia and the patella) not covered by the prosthetic elements, from the opened medullary canal (again, from the femur) and the dissected periarticular soft tissues (especially posteriorly) (1). This may cause a reduction of about 20% in circulating blood volume resulting in major cardiovascular complications and increased mortality. A great number of patients (between 10 and 30%) require red blood cells (RBCs) allogeneic transfusion (2) that may be accompanied by important risks such as allergic reaction, anaphylactic shock, fever, infections (3). Also, allogeneic blood transfusion (ABT) implies high costs, and orthopaedic surgery accounts for over 10% of all ABTs, 40% of which for joint replacement procedures (4,5). In order to reduce blood loss in TKA patients, various methods have been proposed: autologous transfusions (6), hypotensive anaesthesia (7), drainage clamping (8), application of fibrin tissue adhesive (9), compression bandage and cryotherapy (10). Furthermore, systemic or local administration of tranexamic acid (TXA) is a well-known method to reduce bleeding and therefore the need for ABTs after surgery (11,12). The use of antifibrinolytic agents is based on evidence that the surgical trauma, as well as promoting the formation of clots by activating the intrinsic and extrinsic coagulation cascade, also leads to a concomitant activation of the plasminogen which induces a hyperfibrinolytic state that accelerates clot's degeneration, thus increasing bleeding from the surgical site (13).

The TXA is a synthetic derivative of the amino acid lysine that acts as a competitive inhibitor of the activation of plasminogen that interferes with fibrinolysis (14); its intravenous administration during joint replacement reduces post-operative bleeding (15). The theoretical risk of venous thromboembolism (VTE) associated with the use of TXA has not been proven clinically in several trials (16), even with high dosages (17). In contrast, a tendency towards a protective effect against pulmonary embolism has been described, probably linked to the reduced need for RBCs transfusion that is a thrombogenic intervention (16).

The aim of this study was to evaluate the efficacy of systemic intravenous (IV) and local low-dose intra-articular TXA administration in reducing post-operative bleeding, haemoglobin loss and the need for ABT in TKA.

PATIENTS AND METHODS

Patients and study design

Medical records of all patients who underwent TKA between January 2017 and September 2019 at Azienda Ospedaliera Universitaria Senese were retrospectively evaluated. Selection criteria were primary osteoarthritis (OA) of the knee as diagnosis, a single surgeon performing the procedure, same surgical access and technique and same cemented prosthesis, surgery conducted under spinal anaesthesia, non-resurfacing patelloplasty to address the patella, and systemic IV and local intra-articular TXA administration at surgery. Exclusion criteria were cardiovascular comorbidities, diabetes, ongoing anticoagulant/antiaggregant therapy, history of previous VTE or any other condition suggesting a pharmacological prophylaxis other than our standard protocol with low molecular weight heparin (Enoxaparine 4000 IU subcutaneously every 24 hours, starting 12 hours after surgery and going on up to regular crutch-free walking).

Twenty patients were found (group A) that met the selection criteria. A control group with same inclusion and exclusion criteria, except that for the administration of TXA at surgery, was matched for age, gender and body mass index (BMI), and 26 patients were recruited (group B).

All patients gave their written consent to the treatment and anonymous use of data and images for research and academic purposes. At our Institutions, neither the Ethical Committee nor Institutional Review Board approval are needed for retrospective studies.

Methods

Surgery was performed with tourniquet at the root of the high, inflated at 300 mmHg of pressure after the preparation of the sterile field and limb exsanguination by elevation and elastic compression with an Esmark bandage. A medial parapatellar approach was performed in all cases. The femur was prepared at first, with intramedullary instrumentation. The entry point of the femoral rod guide was closed by an autologous

bone plug in all cases, to reduce post-operative bleeding (18). The tibia was prepared with an extramedullary guide.

The same cemented prosthesis was implanted in all cases (Evolution Medial Pivot; Microport, Shangai, China); the femoral component presents an open intercondylar box which eventually does not stop residual bleeding from the femoral canal. A non-resurfacing patelloplasty was performed in all cases (circumferential resection of the osteophytes plus patellar reshaping with resection of the cartilage layer), aiming to improve the congruency between the native patella and the femoral trochlea (19). After cementation of prosthetic components, tourniquet was released, accurate haemostasis was performed, and an intra-articular drainage was positioned.

Patients in group A intra-operatively received TXA according to the proposed protocol: 20 mg/kg in 100 mL of saline solution IV around 10 minutes before release of the pneumatic tourniquet (to allow the drug to reach the plasma peak plasma at the time of release) (15) plus intra-articular application of TXA 1 g after suturing the capsule (so to have a "topic" effect). Patients in group B did not receive TXA at all. Finally, a sterile wound dressing and a bulky compression dressing (so called modified Robert Jones bandages) (20) were applied. No anti-bleeding adjuvant pharmacological actions were undertaken in the post-operative period, and post-operative rehabilitation protocol was the same in both groups. Open suction drainage was left *in situ* for 48 hours after surgery; intermittent cryotherapy was used in the post-operative period (20 minutes every 2 hours for the first 2 post-operative days and after physiotherapy sessions afterwards, *ter in die*), and continuous passive motion was initiated from the first post-operative day (2 hours *bis in die*).

Haemoglobin was measured pre-operatively and at 1, 24, 48 and 72 hours after surgery. ABT criteria for elective orthopaedic surgery were set at our Institution, at haemoglobin level equal to or less than 8 g/dL in healthy patients younger than 80 and haemoglobin level equal to or less than 9 g/dL in patients with cardiovascular comorbidities (exclusion criterion in this study) or age equal to or over 80 years.

Statistical analysis

Patients' age, body mass index (BMI) and haemoglobin values at surgery were assessed for normality (Anderson-Darling test) and compared between groups using the Mann-Whitney U test. The χ^2 test was used to compare gender distribution and the differences in the number of patients requiring ABT. The Mann-Whitney U test was also used to compare fall rates of haemoglobin and the number of transfused RBCs units in the post-operative period. The level of significance was set at $p<0.05$.

RESULTS

Patients' age at surgery was between 51 and 88 years, with an average of 72.8 years; there were 17 males and 29 females. Group A consisted of 20 patients (nine males, 11 females) aging between 51 and 87 (mean 72.5) years old. Group B was composed of 26 patients (eight males, 18 females) with a mean age of 73.1 (range 52 – 88) years old. No significant differences were observed between groups for demographics (age, gender, BMI) and haemoglobin values at surgery.

Two (10%) patients in group A and 16 (61.5%) in group B required ABT (p=0.0004). Each patient in group A received 2 units of RBCs, while in group B, two patients received 1 unit of RBCs each and one patient received 4 units, for a total number of transfused RBCs units of 4 in group A and 32 in group B (p=0.0006).

The decrease in haemoglobin values observed at 48 hours after surgery represented the minimum value recorded in the post-operative period for both groups: in group A there was a decrease ranging from 6.4 to 0.3 g/dL with a mean of 3.54 g/dL, in group B the mean decrease was 4.64 g/dL with a range from 7.2 g/dL to 1.8 g/dL (p=0.0126).

No major side effects or complications in the immediate post-operative period regarding anaemia or ABTs were recorded.

DISCUSSION

The main finding of this study confirmed the efficacy of a combined systemic and local TXA administration to reduce post-operative bleeding and haemoglobin post-operative loss, and subsequent need for ABT, in TKA performed for primary knee OA in patients without cardiovas-

cular comorbidities. Several studies already exist that described the efficacy of TXA administration in joint replacement surgery with special regards to TKAs (1,8,11,12,15,17, 21–25). Also, several meta-analyses have been conducted (16, 26-34), and all studies agreed about the efficacy of TXA against bleeding and confirmed its safety, as well. Unfortunately, their results cannot be easily compared to each other as every single study presented a different protocol of TXA administration with respect to timing, route and/or dosage (Table 1). In the pioneering studies of Hiippala et al. TXA was administered IV towards the end of surgery, after deflating tourniquet, and afterwards also in the immediate post-operative hours, always in IV route (11,12). Sepah et al. also compared IV administration of 2 doses of TXA versus no administration at all (1). Wong et al. found that "topic" TXA administration left *in situ* for 5 minutes at the end of surgery was beneficial with respect to placebo; also, a slightly statistical difference between low-dose (1.5 g) and high-dose (3 g) TXA was present with regards to ABT (21).

Also, different pharmacological VTE prophylaxis were administered, different prostheses were implanted, and different post-operative protocols were used. Ishida et al. compared intra-articular injection of 2 g of TXA versus saline solution left into the joint with a clamped drainage for 30 minutes, but a miscellaneous cohort of prostheses were implanted, some with a closed intercondylar box (22). A great difference in the use of the drainage was present, too: some authors did not use it at all (21), some had the drainage clamped for some period (8,22), some had it open, as in the present study (17). Lastly, some confusion exists in the terminology: which is the difference between "intra-articular" and "topic" administration? These terms can be interpreted as mutual but they are intended in different meaning in different studies: some authors injected the TXA through the drainage (8,22), others poured the TXA into the joint before capsular closure (21,23), others injected the TXA into the joint after capsular closure as in the present study (17,24,25,30) and others both soaked the joint with TXA solution and injected the same solution after capsular closure (15).

Nevertheless, all studies indicated that the administration of TXA is beneficial. Xu et al., in a recent meta-analysis, found that the systemic IV plus local topical administration of TXA showed the lowest relative risk ratio for ABT when compared to "placebo", to routine haemostasis and to other mode of administration; also, no additional benefits were found with increasing dose; the 15 mg/kg IV dose together with 1 g topical dose seems to be sufficient to significantly reduce the need for blood transfusion, and no safety issue was underlined (32).

In conclusion, systemic IV and local topic intra-articular administration of TXA is confirmed as a safe, inexpensive and effective method to reduce post-operative bleeding, drop in haemo-

Table 1. Efficacy of tranexamic acid (TXA) against bleeding in different studies*

Study	Protocol of TXA administration
Hiippala et al. (1995)	IV 15 mg/kg after deflating tourniquet
(RCT double-blinded)	Vs placebo (equal volume of 0.9% sodium chloride solution)
Hiippala et al. (1997)	IV 15 mg/kg after deflating tourniquet + 10 mg/kg x 2 (at 3- and 6-hours post-op)
(RCT double-blinded)	Vs placebo (equal volume of normal saline solution)
Wong et al. (2010)	IA (topic) 1.5 g at the end of surgery for 5 minutes
(RCT double-blinded)	Vs IA (topic) 3 g at the end of surgery for 5 minutes
	Vs placebo (100 mL of normal saline solution) at the end of surgery for 5 minutes
Sepah et al. (2011)	IV 1 g before inflating tourniquet + 1 g after deflating tourniquet
(RCT double-blinded)	Vs nothing
Ishida et al. (2011)	IA (injected) 2 g
(RCT)	Vs placebo (saline)
Onodera et al. (2011)	IA (injected) 1 g + carbazochrome sodium sulfonate hydrate 50 mg + amikacin sulfate 200 mg
(RCT)	Vs saline + amikacin sulfate 200 mg
Seo et al. (2013)	IV 1.5 g
(RCT)	Vs IA (topic) 1.5 g at suture
	Vs saline both IV and IA
Nielsen et al. (2016)	IV 1 g pre-operatively + IA (injected) 3 g after capsular closure
(RCT double-blinded)	Vs IV 1 g pre-operatively + placebo (saline)
Wang et al. (2018	IV 20 mg/kg before inflating tourniquet
(RCT double-blinded)	Vs IA (topic) 1 g before cementation + IA (injected) 1 g at suture
	Vs Oral 2 g 2 hours before surgery
Yuan et al. (2018) (in RTKA)	IV 20 mg/kg 1 hour before surgery + IA (injected) 3 g at suture
(RCT double-blinded)	Vs IA (injected) 3 g at suture
Zhang et al. (2019)	IV 20 mg/kg pre-operatively
(RCT double-blinded)	Vs IA (injected) 3 g after suture
	Vs IV 20 mg/kg pre-operatively + IA (injected) 3 g after suture
Present study	IV 20 mg/kg 10 minutes before deflating tourniquet + IA (injected) 1 g at suture
(retrospective cohort study)	Vs nothing

* Different studies could not be compared with each other as study designs are differed in TXA administration (dose, route, timing)
RCT, randomized clinical trial; IV, intravenous; Vs, versus; IA, intra-articular; RTKA, revision total knee arthroplasty

globin values and the subsequent need for ABT after primary cemented TKA in patients without cardiovascular comorbidities. The routine use of TXA to reduce bleeding can be recommended in joint replacement surgery. Routes of administration can be various, while systemic IV plus local topical seem to be the most effective.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

REFERENCES

1. Sepah YJ, Umer M, Ahmad T, Nasim F, Umer Chaudhry M, Umar M. Use of tranexamic acid is a cost-effective method in preventing blood loss during and after total knee replacement. J Orthop Surg Res 2011; 6:22.
2. Ponnusamy KE, Kim TJ, Khanuja HS. Perioperative blood transfusions in orthopaedic surgery. J Bone Joint Surg Am 2014; 96-A:1836–44.
3. Frisch NB, Wessell NM, Charters MA, Yu S, Jeffries JJ, Silverton CD. Predictors and complications of blood transfusion in total hip and knee arthroplasty. J Arthroplasty 2014; 29(Suppl 9):189–92.
4. Stanworth SJ, Cockburn HAC, Boralessa H, Contreras M. Which groups of patients are transfused? A study of red cell usage in London and southeast England. Vox Sang 2002; 83:352-7.
5. Wells AW, Mounter PJ, Chapman CE, Stainsby D, Wallis JP. Where does blood go? Prospective observational study of red cell transfusion in north England. Br Med J 2002; 325:803-4.
6. Parvizi J, Chaudhry S, Rasouli MR, Pulido L, Joshi A, Herman JH, Rothman RH. Who needs autologous blood donation in joint replacement? J Knee Surg 2011; 24:25-31.
7. 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; 26:105-10.
8. Onodera T, Majima T, Sawaguchi N, Kasahara Y, Ishigaki T, Minami A. Risk of deep venous thrombosis in drain clamping with tranexamic acid and carbazochrome sodium sulfonate hydrate in total knee arthroplasty. J Arthroplasty 2012; 27:105–8.
9. Levy O, Martinowitz U, Oran A, Tauber C, Horoszowski H. The use of fibrin tissue adhesive to reduce blood loss and the need for blood transfusion after total knee arthroplasty. A prospective, randomized, multicenter study. J Bone Joint Surg Am 1999; 81:1580–8.
10. Gibbons C, Solan M, Ricketts D, Patterson M. Cryotherapy compared with Robert Jones bandage after total knee replacement: A prospective randomized trial. Int Orthop (SICOT) 2001; 25:250-2.
11. Hiippala S, Strid L, Wennerstrand M, Arvela V, Mantyla S, Ylinen J, Niemela H. Tranexamic acid (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. Br J Anaesth 1995; 74:534-7.
12. Hiippala ST, Strid LJ, Wennerstrand MI, Arvela JV V, Niemelä HM, Mäntylä SK, Kuisma RP, Ylinen JE. Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. Anesth Analg 1997; 84:839-44.
13. Oremus K. Tranexamic acid for the reduction of blood loss in total knee arthroplasty. Ann Transl Med 2015; 3:1-4.
14. Mannucci PM. Hemostatic drugs. N Engl J Med 1998; 339:245-53.
15. Wang D, Wang HY, Cao C, Li LL, Meng WK, Pei FX, Li DH, Zhou ZK, Zeng WN. Tranexamic acid in primary total knee arthroplasty without tourniquet: a randomized, controlled trial of oral versus intravenous versus topical administration. Sci Rep 2018; 8:1-9.
16. Alshryda S, Sarda P, Sukeik M, Nargol A, Blenkinsopp J, Mason JM. Tranexamic acid in total knee replacement: a systematic review and meta-analysis. J Bone Joint Surg Br 2011; 93:1577-85.
17. Yuan X, Wang J, Wang Q, Zhang X. Synergistic effects of intravenous and intra-articular tranexamic acid on reducing hemoglobin loss in revision total knee arthroplasty: a prospective, randomized, controlled study. Transfusion 2018; 58:982-8.
18. 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; 15:947-9.
19. Cerciello S, Robin J, Lustig S, Maccauro G, Heyse TJ, Neyret P. The role of patelloplasty in total knee arthroplasty. Arch Orthop Trauma Surg 2016; 136:1607–13.
20. Brodell JD, Axon DL, Evarts CM. The Robert Jones bandage. J Bone Joint Surg Br 1986; 68:776-9.
21. Wong J, Abrishami A, El Beheiry H, Mahomed NN, Davey JR, Gandhi R, Syed KA, Hasan SMO, De Silva Y, Chung F. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am 2010; 92:2503-13.
22. Ishida K, Tsumura N, Kitagawa A, Hamamura S, Fukuda K, Dogaki Y, Kubo S, Matsumoto T, Matsushita T, Chin T, Iguchi T, Kurosaka M, Kuroda R. Intra-articular injection of tranexamic acid reduces not only blood loss but also knee joint swelling after total knee arthroplasty. Int Orthop (SICOT) 2011; 35:1639-45.
23. 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 Surgery Sport Traumatol Arthrosc 2013; 21:1869–74.
24. Nielsen CS, Jans Ø, Ørsnes T, Foss NB, Troelsen A, Husted H. Combined intra-articular and intravenous tranexamic acid reduces blood loss in total knee arthroplasty a randomized, double-blind, placebo-controlled trial. J Bone Joint Surg Am 2016; 98:835-41.

25. Zhang YM, Yang B, Sun XD, Zhang Z, Figueiredo N. Combined intravenous and intra-articular tranexamic acid administration in total knee arthroplasty for preventing blood loss and hyperfibrinolysis: A randomized controlled trial. Med (United States) 2019; 98:1-8.
26. Yang Z-G, Chen W-P, Wu L-D. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. J Bone Joint Surg Am 2012; 94:1153-9.
27. 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 Surgery Sport Traumatol Arthrosc 2012; 20:1742-52.
28. Panteli M, Papakostidis C, Dahabreh Z, Giannoudis PV. Topical tranexamic acid in total knee replacement: A systematic review and meta-analysis. Knee 2013; 20:300-9.
29. Tan J, Chen H, Liu Q, Chen C, Huang W. A meta-analysis of the effectiveness and safety of using tranexamic acid in primary unilateral total knee arthroplasty. J Surg Res 2013; 184:880-7.
30. Yuan ZF, Yin H, Ma WP, Xing DL. The combined effect of administration of intravenous and topical tranexamic acid on blood loss and transfusion rate in total knee arthroplasty: combined tranexamic acid for TKA. Bone Joint Res 2016; 5:353-61.
31. Fillingham YA, Ramkumar DB, Jevsevar DS, Yates AJ, Shores P, Mullen K, Bini SA, Clarke HD, Schemitsch E, Johnson RL, Memtsoudis SG, Sayeed SA, Sah AP, Della Valle CJ. The efficacy of tranexamic acid in total knee arthroplasty: a network meta-analysis. J Arthroplasty 2018; 33:3090-8.
32. Xu S, Chen JY, Zheng Q, Lo NN, Chia SL, Tay KJD, Pang HN, Shi L, Chan ESY, Yeo SJ. The safest and most efficacious route of tranexamic acid administration in total joint arthroplasty: A systemic review and network meta-analysis. Thromb Res 2019; 176:61-6.
33. Sun Q Li J, Chen J, Zheng C, Liu C, Jia Y. Comparison of intravenous, topical or combined routes of tranexamic acid administration in patients undergoing total knee and hip arthroplasty: A meta-analysis of randomised controlled trials. BMJ Open 2019; 9:1-14.
34. Moskal JT, Capps SG. Intra-articular tranexamic acid in primary total knee arthroplasty: meta-analysis. J Knee Surg 2018; 31:56-67.