The combined intrarticular/intravenous administration of tranexamic acid in cemented total knee arthroplasty

P. K. Karampinas[1], J. A. Vlamis[3], M. Mpakalakos[3], E. G. Papadelis[2], K. Adamidou-Lampropoulou[1], Sp. Pneumatikos[3]

[1] *Athens Medical Center, Greece,* [2]*Hampshire Hospital, NHS Trust*
[3] *3rd University Orthopaedic Department of Athens, KAT Hospital*

ABSTRACT

Total knee and hip arthroplasty is the commonest reason for transfusion in patients undergoing elective surgery and accounts for 9.8% of all transfused red blood cell units. However, Blood transfusions are associated with increased risks of immunological reactions, transmission of diseases and infections. In recent years pharmacological agents become more popular in management of perioperative and postoperative bleeding. Tranexamic acid (TXA), a synthetic analogue of the amino acid lysine, is a fibrinolysis inhibitor which acts by blocking the lysine binding site of plasminogen that induces blood loss. The purpose of this study was to evaluate the efficacy of combined intravenous and intra-articular administration of TXA in regard to postoperative blood loss and transfusion requirements following TKA.

KEY WORDS: total knee arthroplasty; blood loss; blood transfusion; tranexamic acid

Introduction

Total knee arthroplasty (TKA) is one of the most common surgical procedures for patients with advanced osteoarthritis. Incidence rate of TKA is expected to increase by 69% in 2050 compared to 2012 [1]. Although TKA relieves knee pain, improves function and patient's quality of life, perioperative bleeding remains one of the main concerns [2]. Total knee and hip arthroplasty is the commonest reason for transfusion in patients undergoing elective surgery and accounts for 9.8% of all transfused red blood cell units [3]. Blood transfusions are associated with increased risks of immunological reactions, transmission of diseases and infections [4]. In recent years pharmacological agents become more popular in management of perioperative and postoperative bleeding. Tranexamic acid (TXA), a synthetic analogue of the amino acid lysine, is a fibrinolysis inhibitor which acts by blocking the lysine binding site of plasminogen that induces blood loss [5]. Recent studies and meta-analysis have shown that TXA can reduce the amount of drainage, total blood

CORRESPONDING AUTHOR, GUARANTOR

Karampinas Panagiotis
Distomou 5-7, Marousi, 15125, Athens, Greece
Tel. +301-6944647789
E-mail. karapana@yahoo.com

VOLUME 69 | ISSUE 2 | APRIL - JUNE 2018

loss and requirement of allogenic transfusion in TKA, without increasing the risk of adverse events such as thromboembolic complications [6]. However it is not established which administration route is more effective. Various dosing regimens have been used for TXA, including intravenous (IV), intra-articular (IA) and combined application of TXA (IV and IA).

Thus, the purpose of this study was to evaluate the efficacy of combined intravenous and intra-articular administration of TXA in regard to postoperative blood loss and transfusion requirements following TKA.

Material and methods

A prospective randomized controlled study was conducted from March 2014 until March 2017. Patients with a diagnosis of primary osteoarthritis undergoing unilateral TKA and able to give informed consent were eligible for inclusion in the study. The exclusion criteria were as follows: allergy to TXA, history of previous surgery on the operated knee, thrombocytopenia, and anemia [hemoglobin (Hb) <10 g/dl], warfarin therapy, coagulopathy, VTE, or major comorbidities (ischemic heart disease, cerebrovascular accident, liver cirrhosis, end-stage renal disease). Written informed consent was obtained from all patients. A total of 172 patients were enrolled in the study and divided into four groups. The randomization concluded with 65 patients in group A (35 females and 30 males), 33 patients in group B (23 females and 10 males), 44 in group C (28 females and 16 males) and 30 patients in group D (18 females and 12 males) with similar demographic characteristics (age, BMI, severity of osteoarthritis, knee angle deformation, ASA). In group A (intraarticular (IA) group) were introduced intraarticular through the drainage 20 ml of saline solution, containing 1,000 mg of tranexamic acid. The patients who were randomized into group B (intravenous (IV) group) received administration of TXA 10 mg/kg intravenously during the induction of anesthesia and before inflation of the tourniquet. Patients assigned to group C (combined group) were given 10 mg/kg tranexamic acid intravenously during the induction of anesthesia and before inflation of the tourniquet and intraarticular through the drainage 20 ml of saline solution, containing 1,000 mg of tranexamic acid. In group D (control group) patients received 20 mL of normal saline using intraarticular application intraoperatively after joint capsule closure and normal saline intravenously during the induction of anesthesia.

All surgical procedures were performed by the same surgical team using the standard medial parapatellar approach and under spinal anesthesia. All TKAs were unilateral and were cemented using the same prosthesis (EVOLUTIONTM Medial pivot knee-WrightR). An intramedullary alignment rod was used for femoral preparation and an extramedullary guide system for tibia preparation. A tourniquet was inflated to a pressure of 300 mmHg before the incision. The tourniquet was not released until skin closure and the application of a compressive dressing. One intra-articular drain was used with open drainage (i.e., without compression of the bag) during the first 48 h after surgery. The drain remained closed for 2 hours postoperatively and subsequently the amount of drain blood loss was recorded. The drains were removed on the second postoperative day (POD) no matter what the drain output was. The postoperative rehabilitation program included continuous passive motion of the knee and muscle strengthening exercise after returning to the ward, and routine mobilization on the first POD. In order to prevent venous thromboembolic event, LMWH was given on the first postoperative day and for duration of 30 days after surgery. The criteria for discharge were a clean wound without discharge and the ability to walk with walker support.

Preoperative data including Hb levels, hematocrit (Hct) levels, prothrombin time (PT), activated partial thromboplastin time (APTT), and platelet count were collected. Outcome measurements included postoperative Hct/Hb levels, Hct/Hb drop, total drain amount, total blood loss, and transfusion rate. We checked Hb level on post-operative day (POD) 1 until 4. We assumed that the blood volume was normalized on POD 4. Total Hb loss was calculated by

VOLUME 69 | ISSUE 2 | APRIL - JUNE 2018

TABLE 1. *Study Groups*

	Group A (TRX IA)	Group B (TRX IV)	Group C (TRX COMP)	Group (control)
Age	71.3 years (range 69-82)	70.7 years (range35-80)	73.9 years (range 63-80)	70.3 years (range 40-87)
Sex	35 Female/30Male	23 Female/10Male	28 Female/16Male	18 Female/12Male
BMI	29.5	32	35	29.4
TKA	65	33	44	30

TABLE 2. *P values of confronting groups*

Combine *vs.* Intravenous	*t*	4.05
	p	0.0022
Combine *vs.* Intraarticular	*t*	1.41
	p	0.18
Combine *vs.* Control	*t*	7.56
	p	1.90E-05
Intravenous *vs.* Control	*t*	8.72
	p	0.00001
Intraarticular *vs.* Control	*t*	0.848
	p	0.00001

subtracting the Hb level on POD 4 from the preoperative level. Total blood loss was calculated from the maximum Hb loss and the amount of blood transfusion. Blood loss was calculated by subtracting the amount of drainage from total blood loss. The hemoglobin cut-off value for allogenic blood transfusion was 8 g/dl in symptomatic patients. All patients were screened for deep vein thrombosis using the clinical symptoms including the presence of Homan's sign and lower leg swelling for 90 days postoperative.

Statistical analyses were performed using SPSS Software (Version 20.0 for Windows, IBM Corp, Armonk, NY, USA), and p values less than 0.05 were considered significant.

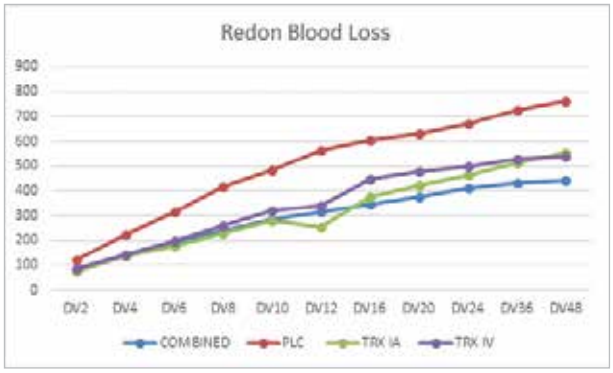
Results

One hundred and seventy two patients were enrolled and completed the study. The demographic data are presented in **table 1**. There was no significant difference in demographic data between the groups. The mean blood loss was calculated with Burke's formula in group A 29.1%, group B 30%, group D 33.6% and group C 13.2%. The difference was statistically significant for the combined administration of tranexamic acid. Total drain amount was significantly lower in the combined group compared to the IV and control group but **not to the intraarticular group (Table 2, Graphic 1**). Significant differences were also observed in total drain amount between IA or IV administration of tranexamic acid and control group as presented in **table 3**. More precisely the mean values of total drain amount in combined group was 440mL while for group A (IA group), group B (IV group) and group D (control group) were 554.2, 537 and 763 mL, respectively. Likewise, the minimum Hb level was recorded on postoperative day 2 for all four groups and the mean values were 11.2 g/dL in group A, 11.3 g/dL in group B, 12.4 g/dL in group C and 11 g/dL in group D (**Graphic 2, 3**). Finally one patient in the group B (IV group) and two patients in the control group D received transfusion with 1 unit of red blood cells during hospitalization. No thromboembolic complications were observed within 90 days postoperatively.

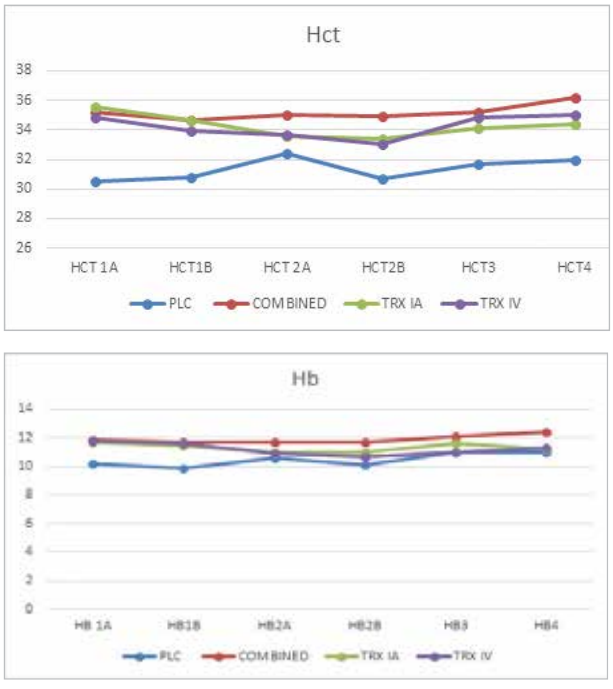
VOLUME 69 | ISSUE 2 | APRIL - JUNE 2018

TABLE 3. *Postoperative Hct/Hb variations and redon blood loss*

	Group A (TRX IA)	Group B (TRX IV)	Group C (TRX COMP)	Group D (Control)
Blood loss (Redon 48h)	554.2 cc	537 cc	440 cc	763 cc
Lower M. Hct/Hb	33.4/11	33/10.7	34.9/11.7	30.5/9.9
Discharged M. Hct/Hb	34.4/11.2	35/11.3	36.2/12.4	32/11
Transfusions	1	0	0	2



Graphic 1: *Redon catheter blood loss during 48h of hospitalization*



Graphic 2: *Variations of Hct and Hb during 48h hospitalization*

Discussion

Total knee arthroplasty may be associated postoperatively with considerable blood loss and the need of transfusion is associated with risk of immunologic reactions and disease transmission with additional costs [7, 8]. The use of tranexamic acid through any route of administration (intravenous (IV), intraarticular (IA) and combined) reduce the need of blood transfusion after total knee arthroplasty without any symptomatic thromboembolic complications [9, 10]. However the ideal route of administration remains debatable. The main finding of this study was the significantly reduced total blood loss noted for combined IV and IA TXA compared with IV or IA TXA monotherapy and placebo. Our study confirms that the combination of IA and IV administration of TXA seems to be more efficient in management of perioperative and postoperative bleeding. Moreover, TXA use is safe regarding the incidence of symptomatic DVT and PE. Theoretically drainage clamping can result in temporary hemostasis while no-clamping leads to control of the hematoma formation, edema and swelling of the knee. When tranexamic acid was administrated no need of postoperative drainage clamping was required [11]. Conservation of blood products, reduced laboratory costs, and shorter hospital stays are likely advantages associated with TXA use, driving cost savings [12, 13]. In our study postoperative hemorrhage and blood loss were significantly reduced using combined intravenous and intraarticular administration of tranexamic acid. Specifically, combined administration of tranexamic acid

VOLUME 69 | ISSUE 2 | APRIL - JUNE 2018

in patients undergoing total knee arthroplasty was associated with significantly reduced total blood loss, transfusion requirements, postoperative hemoglobin decline and length of stay compared to single application alone. Nonetheless, it was not associated with prolonged operation time. Moreover, no adverse effects, such as superficial infection, deep vein thrombosis or pulmonary embolism, were observed with tranexamic acid use. It has been suggested by the literature that combined administration of TXA demonstrated excellent clinical efficacy and safety in patients with total knee arthroplasty [14]. The clamping of drain combined with tranexamic acid administration could reduce postoperative blood loss and blood transfusion after TKA, significantly more than using tranexamic acid or drain clamping alone. There were some limitations in this study. First, no ultrasonography was done to assess asymptomatic deep vein thrombosis, nor routine screening for pulmonary embolism. However, all patients were screened for thromboembolic complications based on their clinical symptoms during follow-up. Second, patients receiving anticoagulants were excluded from the study and thus our results cannot be expanded on those patients. Finally, there was high female-to-male ratio, because most patients who undergo TKA in Greece are female, nevertheless the female-to-male ratio was not different between the four groups.

Conclusion

The use of intraarticular in combination with intravenous administration of tranexamic acid is an efficient and safe method to control postoperative blood loss, hemorrhage and minor bleeding complications.

Conflict of interest:

The authors declared no conflicts of interest.

VOLUME 69 | ISSUE 2 | APRIL - JUNE 2018

REFERENCES

1. Inacio M, Paxton E, Graves S, Namba R, Nemes S. Projected increase in total knee arthroplasty in the United States – an alternative projection model. *Osteoarthritis and Cartilage* 2017; 25: 1797-1803.
2. Park J, Rasouli M, Mortazavi S, Tokarski A, Maltenfort M, Parvizi J Predictors of Perioperative Blood Loss in Total Joint Arthroplasty. *The Journal of Bone and Joint Surgery-American* 2013; 95: 1777-1783.
3. Harwin S, Kapadia B, Issa K, Mont M Blood Management Strategies in Total Knee Arthroplasty. *Journal of Knee Surgery* 2013; 26: 371-372.
4. Shortt J, Polizzotto M, Waters N, Borosak M, Moran M, Comande M, Devine A, Jolley D, Wood E Assessment of the urgency and deferability of transfusion to inform emergency blood planning and triage: The Bloodhound prospective audit of red blood cell use. *Transfusion* 2009; 49: 2296-2303.
5. Melvin J, Stryker L, Sierra R Tranexamic Acid in Hip and Knee Arthroplasty. *Journal of the American Academy of Orthopaedic Surgeons* 2015; 23: 732-740.
6. Yuan Z, Yin H, Ma W, Xing D The combined effect of administration of intravenous and topical tranexamic acid on blood loss and transfusion rate in total knee arthroplasty. *Bone & Joint Research* 2016; 5: 353-361.
7. Frisch N, Wessell N, Charters M, Yu S, Jeffries J, Silverton C Predictors and Complications of Blood Transfusion in Total Hip and Knee Arthroplasty. *The Journal of Arthroplasty* 2014; 29: 189-192.
8. Sinclair K, Clarke H, Noble B Blood Management in Total Knee Arthroplasty: A Comparison of Techniques. *Orthopedics* 2009; 32: 19-8.
9. Charoencholvanich K, Siriwattanasakul P. Tranexamic Acid Reduces Blood Loss and Blood Transfusion after TKA: A Prospective Randomized Controlled Trial. *Clinical Orthopaedics and Related Research* 2011; 469: 2874-2880.
10. Shen P, Hou W, Chen J, Wang B, Qu Y Effectiveness and Safety of Tranexamic Acid for Total Knee Arthroplasty: A Prospective Randomized Controlled Trial. *Medical Science Monitor* 2015; 21: 576-581.
11. Wu Y, Yang T, Zeng Y, Li C, Shen B, Pei F Clamping drainage is unnecessary after minimally invasive total knee arthroplasty in patients with tranexamic acid. *Medicine* 2017; 96: e5804.
12. Lin Z, Woolf S Safety, Efficacy, and Cost-effectiveness of Tranexamic Acid in Orthopedic Surgery. *Orthopedics* 2016; 39: 119-130.
13. Goyal N, Chen D, Harris I, Rowden N, Kirsh G, MacDessi S Clinical and Financial Benefits of Intra-Articular Tranexamic Acid in Total Knee Arthroplasty. *Journal of Orthopaedic Surgery* 2016; 24: 3-6.
14. Li J, Li H, Zhao H, Wang J, Liu S, Song Y, Wu H Combined use of intravenous and topical versus intravenous tranexamic acid in primary total knee and hip arthroplasty: a meta-analysis of randomised controlled trials. *Journal of Orthopaedic Surgery and Research* 2017; 12: 11. Published online 2017 Jan 19. doi: 10.1186/s13018-017-0512-4.

VOLUME 69 | ISSUE 2 | APRIL - JUNE 2018

READY - MADE CITATION

Karampinas P K, Vlamis J A, Mpakalakos M, Papadelis E G , Adamidou-Lampropoulou K, Pneumatikos Sp. The combined intrarticular/intravenous administration of tranexamic acid in cemented total knee arthroplasty. *Acta Orthop Trauma Hell* 2018; 69(1): 22-28.

ΠΕΡΙΛΗΨΗ

Η ολική αρθροπλαστική γόνατος είναι μια από τις συχνότερα πραγματοποιούμενες ορθοπαιδικές επεμβάσεις κατά την οποία απαιτείται η μετάγγιση αίματος λόγω της απώλειας που συμβαίνει διεγχειρητικά και άμεσα μετεγχειρητικά.. Δεδομένων των προβλημάτων που μπορεί να προκύψουν από την ετερόλογη μετάγγιση αίματος όπως ανοσοαντιδράσεις, μετάδοση νοσημάτων και λοιμώξεων, και των δυσκολιών που προκύπτουν από την αυτόλογη παρακαταθήκη αίματος, η χρήση του τρανεξαμικού οξέος διεγχειρητικά αποτελεί μια εναλλακτική λύση. Το τρανεξαμικό οξύ αποτελεί συνθετικό ανάλογο του αμινοξέος της λυσίνης που λειτουργεί ως αναστολέας ινοδώλυσης. Σκοπός της κλινικής αυτής μελέτης είναι η αξιολόγηση της συνδυασμένης ενδοφλέβιας και ενδοαρθρικής έγχυσης τρανεξαμικού οξέος σε ασθενείς που υποβλήθηκαν σε ολική αρθροπλαστική γόνατος και ο βαθμός ελάττωσης της ανάγκης μετάγγισης αίματος.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: ολική αρθροπλαστική γόνατος, μετάγγιση αίματος τρανεξαμικό οξύ