



© J ORTHOP TRAUMA SURG REL RES
14(1) 2019

Research Article

Efficacy of topical and intravenous tranexamic acid (txa) in reducing blood loss in primary total knee arthroplasty, a prospective randomized trial

AHMED KHALIFA (1), MOHAMMAD A MAHRAN (2), MOHAMMAD K ABDELNASSER (2), HATEM M BAKR (2), YASER E KHALIFA (2), AHMED M ABDELAAL (2), GALAL ZAKI SAID (2)

(1) Qena University Hospital Qena, Egypt

(2) Orthopaedic and Traumatology Department, Assuit University Hospital, Assuit, Egypt

Address for correspondence:

Ahmed Khalifa

FRCS (Tr&Ortho), MSc Qena University Hospital Qena, Egypt

khalifaahmed8486@yahoo.com

Statistics

Figures	02
Tables	03
References	22

Received: 26.11.2018

Accepted: 26.12.2018

Published: 03.01.2019

Abstract

Introduction: Total Knee Arthroplasty (TKA) is a major Orthopaedic operation that involves significant blood loss due to extensive soft tissue release and bone cuts. Fibrinolysis is considered the major cause of postoperative bleeding after TKA surgery, pharmacologic agents such as (Tranexamic Acid) TXA, a plasminogen-activator inhibitor, have been employed to reduce perioperative blood loss and prevent the need for post-operative transfusion.

Patients and methods: A prospective randomized study involving 75 patients over a period of 6 month in our arthroplasty unit at a tertiary referral orthopedic hospital. The patients were divided into three groups, 25 patients in each one. GI received 2 gms of intravenous TXA before tourniquet inflation, GII received 3 gms TXA in 100 ml saline intraarticular (topical) after capsular closure, GIII was a control group. The primary outcome measure was perioperative blood loss. Hemoglobin levels at day two postoperative and thromboembolic complications as the secondary outcomes.

Results: The mean blood loss was 970.48 ml in the control group, while it was 618.84 ml and 683.84 ml in GI and GII TXA groups respectively, there was significant statistical difference ($P < 0.05$) between GI and GIII; and between GII and GIII. There was no significance difference in blood loss in topical versus intravenous TXA groups.

Conclusion: TXA both local and intravenous are effective in reducing blood loss in TKA compared to no TXA usage.

Keywords: TXA, TKA, tranexamic acid, total knee arthroplasty, blood loss

INTRODUCTION

Total Knee Arthroplasty (TKA) usually done with the use of tourniquet resulting in unapparent intraoperative bleeding with the possibility of subsequent postoperative blood loss which may range between 500 to 1000 cc [1].

Blood loss requiring transfusion to increase hemoglobin (Hb) level has been reported after unilateral TKA, with incidence ranging from 11% to 67% [2,3]. Although it may be mandatory, it is not risk free, in addition to well-known risks, such as volume overload, mis-transfusion, the transmission of infections, transfusion related acute lung injury, allergic transfusion reactions, or alloimmunization [4], there is also increased morbidity and mortality, and longer hospital stay [5].

As hyper-fibrinolysis is considered the major cause of postoperative bleeding after TKA surgery [6], pharmacologic agents such as Tranexamic Acid (TXA), a plasminogen-activator inhibitor, have been employed to reduce perioperative blood loss and prevent the need for post-operative transfusion. Reports on IV TXA show both clinical efficacy and an acceptable safety profile, with no increased rate of infections or thromboembolic events [7-11].

This study was designed to assess the efficacy of topical and intravenous (IV) use of TXA compared to a control group in primary TKA. Our hypothesis is that its use is effective in reducing perioperative blood loss with minor change in postoperative hemoglobin level and without increase risk of Venous Thromboembolism (VTE).

METHODS

This study was exempt according to the institutional review board (ethical committee) of our institution. Informed consent was obtained from the patients following the guidelines set forth by our institution and by the Declaration of Helsinki and Good Clinical Practice.

A prospective randomized study comprising 75 patients undergoing primary unilateral total knee arthroplasty were recruited over a period of 6 months in our arthroplasty unit starting from January 2018.

Patients data were collected including: Demographics (sex, age, BMI), preoperative and day 2 postoperative hemoglobin level and during hospital stay venous thromboembolic events.

Patients diagnosed as primary OA of the knee with physical status of I-III according to the American Society of Anesthesiologists (ASA) were included in this study, patients with inflammatory arthritis, post-traumatic arthritis, previous history of knee surgery, history of thromboembolic disease, chronic renal failure, and anemia preoperatively (HB<10 gm/L) were excluded.

The surgical technique was standardized and all procedures were done by the 2 senior surgeons.

Under full monitoring, all patients received Spinal anesthesia. With the use of laryngeal mask airway when necessary, and a tourniquet was inflated 150 mmHg above the systolic blood pressure in all the patients.

1st generation cephalosporin was given for all cases 30 min before tourniquet inflation. An anterior midline skin incision and a standard medial parapatellar approach was utilized in all cases. Intra-medullary guides were used for distal femoral and proximal tibial cuts. To reduce the intra-operative blood loss from the femoral hole, an intra-medullary plug with bone graft was used. Cemented

posterior cruciate substitution prosthesis was used in all cases. The patella was not resurfaced in all cases. After cementation of all components and placement of final polyethylene, the placement of a deep drain and closure of the arthrotomy, the drain was clamped for 1 hour postoperatively, after which it was released and kept open for 24 hours then removed. Patients were randomly allocated into 3 groups:

Group I: Received IV TXA in a dose of 2 gms at anesthesia induction before tourniquet inflation

Group II: Received intraarticular injection (topical) of TXA in a dose of 3 gms in 100 ml normal saline after capsular closure

Group III: Didn't receive TXA (control group)

Blood loss was estimated by Weighing Method (weighing of dry surgical swabs before and at the end of surgery and the difference would be the blood absorbed by the swabs) added to the amount of the blood in the suction tubing (after subtracting amount of saline used for wash) added to the volume of blood in the drain by the end of 24 hrs.

All patients received low molecular weight heparin prophylaxis post-operatively during hospital stay, all patients were mobilized at the same day of surgery as tolerated.

STATISTICAL ANALYSIS

Data were collected and analyzed by computer program SPSS "ver. 21" Chicago. USA. Data were expressed as mean, Standard Deviation, and number and percentage. Mann-Whitney was used to determine significance for numeric variable. Chi. Square was used to determine significance for categorical variable. ANOVA test was used to compare significance between the three groups. *P value of <0.05 is significant.

RESULTS

There was no difference in age, BMI, ASA status and pre-operative hemoglobin levels in the 3 studied groups (Table 1).

The mean blood loss was significantly more in the control group than in those who received TXA (P<0.05). The mean blood loss was 970.48 ml in the control group versus 618.84 ml, 683.84 ml in GI and GII TXA groups respectively. There was no significant difference in blood loss between systemic (GI) and topical (GII) TXA groups (Table 2 and Fig. 1).

The drop-in hemoglobin level was significantly lower in patients receiving TXA (GI and GII) than in the control (GIII) group (P<0.001), with no significant difference between topical and intravenous TXA (Table 3), in (GIII) there was significant difference in Hb level before and after surgery (P<0.05). No blood transfusion needed for any patient in the three groups. There were no venous

Table 1. Demographic data in study groups

	TXA IV (G I =25)	TXA topical (G II =25)	Control (GIII=25)	P value
1-Age (years)	56.96 ± 11.42	54.14 ± 8.92	50.60 ± 9.40	0.737
2- Sex:				
• Male	9 (36.0%)	11 (44.0%)	16 (64.0%)	0.842
• Female	16 (64.0%)	14 (56.0%)	9 (36.0%)	
3- BMI (Kg/m ²)	31.34 ± 2.45	30.22 ± 3.22	32.35 ± 2.33	0.517

Table 2. Blood loss in study groups

Total	TXA IV (G I)	TXA topical (G II)	Control (GIII)	P value
Blood loss (ml)	618.84 ± 126.90	683.84 ± 111.65	970.48 ± 142.60	<0.05

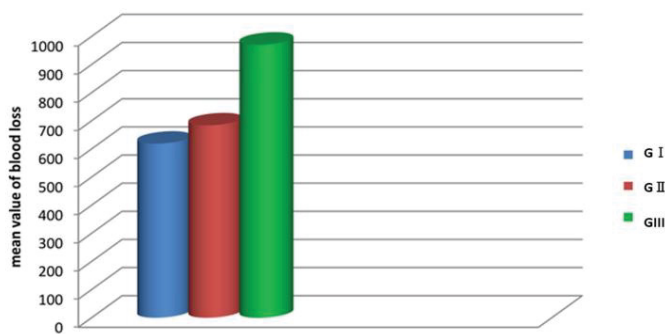


Fig. 1. Total blood loss in study groups

Table 3. Hemoglobin (Hb) changes in study groups

	TXA IV (G I)	TXA topical (G II)	Control (GIII)	P value
1- Hb before op.	12.96 ± 1.46	12.83 ± 1.36	12.56 ± 1.56	0.539
2- Hb. day 2 post op.	11.19 ± 0.96	11.92 ± 0.94	9.22 ± 0.75	<0.001

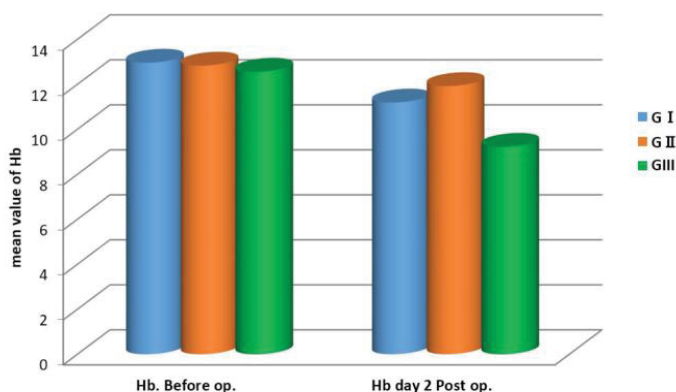


Fig. 2. Hemoglobin change in study groups, (Hb: Hemoglobin, Post op: postoperative)

thromboembolic complications reported in any patient in this study during hospital stay (Fig. 2).

DISCUSSION

TXA is an analog of the amino acid lysine. It competitively inhibits plasminogen activation and plasmin binding to fibrin, thus inhibiting fibrin degradation. Since it works by reducing breakdown of fibrin once formed, it is not procoagulant per se but rather supportive of coagulation already in progress. This makes it potentially well suited for use in reducing postoperative bleeding, where surgical hemostasis has been achieved and fibrinolytic activity needs to be suppressed to help maintain hemostasis without promoting venous thrombus formation.

Results of our study are comparable to those reported in the literature for both intravenous and topical use of TXA as an efficient way to reduce blood loss perioperatively in comparison to no TXA usage.

Wong et al., reported a reduction of blood loss by 20 to 25% in comparison to placebo with a topical technique [12].

Fu et al. performed a meta-analysis of 22 randomized controlled studies on IV use of TXA and found that its use resulted in a significant reduction in blood loss, transfusion rates, and volume of blood transfused [13].

Seo et al., in a prospective study comparing intravenous TXA,

intra-articular TXA, and placebo (50 patients each group) found superior results with intraarticular TXA than IV TXA [14].

Akizuki et al., first reported topical use of TXA in orthopedic surgery in 1997, reporting no postoperative blood transfusions in 42 simultaneous bilateral cementless TKA patients and 64 unilateral cementless TKA patients, this report did not appeal to many surgeons, or they were not aware of it, because it was not until 2010 when another group reported on the use of topical TXA in TKA [12-18].

Blood loss prevention has a major influence on cost of total knee replacement through decrease in morbidity, mortality, complications, and length of hospital stay [15]. Blood transfusion is the most important predictor of increased length of stay after total knee replacement; in a previous study in which the mean length of stay following “fast-track” knee replacement was only 3.8 days, while the length of stay for the 12% of patients who required a transfusion was threefold greater than that mean [16,17]. Several reviews and meta-analyses of published randomized controlled trials have provided level I evidence that intravenous TXA reduces blood loss and the need for transfusion without increasing the rate of adverse events [19-21].

Despite the significant literature support for the use of TXA in TKA, many common medical conditions, including renal insufficiency, history of previous DVT, cardiac and cerebrovascular disease may preclude the use of IV TXA at the time of surgery, these same contraindications may not apply to the topical use of TXA, perhaps due to the presumed delay in systemic absorption after application into the knee joint [9].

It is hypothesized that intravenous TXA is distributed throughout the whole circulating volume there by reducing its therapeutic concentration at the site of bleeding (the joint cavities of hip or knee), while topically applied TXA is predominantly distributed in the joint cavity and thus reaches a higher therapeutic concentration at the site of bleeding. Topical application leads to 70% lower systemic absorption and plasma concentration than an equivalent dose of intravenous injections, and may therefore be a safer alternative to giving it systemically [12,22].

Topical intra-articular TXA could be helpful to patients with contraindications to systemic TXA, as absorption from the joint is clinically negligible [12].

Our study had some limitations, the small number of patients included in each group, we also didn’t report about complications which may occur at the early period after patient discharge from the hospital like wound healing problems or any incidence of thromboembolic events after patient discharge.

CONCLUSION

TXA succeeded in reducing blood loss in TKA. There was no significance difference in blood loss in topical and intravenous TXA groups with no significant drop in hemoglobin level as well as no venous thromboembolic events.

Further study is needed to compare the safety profiles of topical versus intravenous TXA in high risk groups.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

References

1. Woolson S.T., Wall W.W.: Autologous blood transfusion after total knee arthroplasty: a randomized, prospective study comparing predonated and postoperative salvage blood. *J Arthroplasty*. 2003;18:243-249.
2. Bierbaum B.E., Callaghan J.J., Galante J.O., et al.: An analysis of blood management in patients having a total hip or knee arthroplasty. *J Bone Joint Surg Am*. 1999;81:2.
3. Noticewala M.S., Nyce J.D., Wang W., et al.: Predicting need for allogeneic transfusion after total knee arthroplasty. *J Arthroplasty*. 2012;27:961.
4. Kleinert K., Theusinger O.M., Nuernberg J., et al.: Alternative procedures for reducing allogeneic blood transfusion in elective orthopaedic surgery. *HSS J*. 2010;6:190-198.
5. Wu W.C., Trivedi A., Friedmann P.D., et al.: Association between hospital intraoperative blood transfusion practices for surgical blood loss and hospital surgical mortality rates. *Ann Surg*. 2012;225:708-714.
6. Cid J., Lozano M.: Tranexamic acid reduces allogeneic red cell transfusions in patients undergoing total knee arthroplasty: results of a Meta-analysis of randomized controlled trials. *Transfusion*. 2005;45:1302-1307.
7. 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.
8. Zhang H., Chen J., Chen F., et al.: The effect of tranexamic acid on blood loss and use of blood products in total knee arthroplasty: a meta-analysis. *Knee Surg Sports Traumatol Arthrosc*. 2012;20:1742.
9. Dahuja A, Dahuja G, Jaswal V, et al.: A prospective study on role of tranexamic acid in reducing postoperative blood loss in total knee arthroplasty and its effect on coagulation profile. *J Arthroplasty*. 2013;29:733.
10. Karam J.A., Bloomfield M.R., Diiorio T.M., et al.: Evaluation of the efficacy and safety of tranexamic acid for reducing blood loss in bilateral total knee arthroplasty. *J Arthroplasty*. 2014;29:501.
11. Tan J., Chen H., Liu Q., et al.: A meta-analysis of the effectiveness and safety of using tranexamic acid in primary unilateral total knee arthroplasty. *J Surg Res*. 2013;184:880.
12. Wong J., Abrishami A., Beheiry H., et al.: Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. *J Bone Joint Surg Am*. 2010;92:2503-2513.
13. Fu D.J., Chen C., Guo L., et al.: Use of intravenous tranexamic acid in total knee arthroplasty: a meta-analysis of randomized controlled trials. *Chin J Traumatol*. 2013;16:67-76.
14. Seo J.G., Moon Y.W., Park S.H., et al.: The comparative efficacies of intra-articular and iv tranexamic acid for reducing blood loss during total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc*. 2013;21:1869.
15. Wong J., Abrishami A., Beheiry H., et al.: Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. *J Bone Joint Surg Am*. 2010;92:2503-2513.
16. Husted H., Holm G., Jacobsen S.: Predictors of length of stay and patient satisfaction after hip and knee replacement surgery: fast-track experience in 712 patients. *Acta Orthop*. 2008;79:168-173.
17. Husted H., Lunn T.H., Troelsen A., et al.: Why still in hospital after fast-track hip and knee arthroplasty? *Acta Orthop*. 2011;82:679-684.
18. Akizuki S., Yasukawa Y., Takizawa T.: A new method of hemostasis for cementless total knee arthroplasty. *Bull Hosp Jt Dis*. 1997;56:222-224.
19. Sukeik M., Alshryda S., Haddad F., et al.: Systematic review and metaanalysis of the use of tranexamic acid in total hip replacement. *J Bone Joint Surg (Br)*. 2011;93-B:39-46.
20. Alshryda S., Sarda P., Sukeik M., et al.: Tranexamic acid in total knee replacement: a systematic review and meta-analysis. *J Bone Joint Surg (Br)*. 2011;93-B:1577-1585.
21. Henry D.A., Carless P.A., Moxey A.J., et al.: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev*. 2007;4:CD001886.
22. De Bonis M., Cavaliere F., Alessandrini F., et al.: Topical use of tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebo controlled study. *J Thorac Cardiovasc Surg*. 2000;119:575-580.