Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Critical Care Medicine

Effect of Tranexamic Acid in Reducing Perioperative Bleeding in Primary Total Knee Arthroplasty (TKA): A Prospective Randomized Study

Houba Abdelhafid[1*], Fjouji Salaheddine[1], Kartite Noureddine[1], Chagar Belkacem[2], Doghmi Nawfal[1]

[1]Department of Critical Care Medicine, Military Hospital Of Instruction Mohammed V of Rabat, Faculty of Medicine and Pharmacy of Rabat, University Mohammed V, Rabat, Morocco
[2]Department of Orthopaedic Surgery, Military Instruction Hospital Mohammed V of Rabat, Faculty of Medicine and Pharmacy of Rabat, University of Mohammed V, Souissi, Rabat, Morocco

DOI: 10.36347/sjams.2022.v10i06.005 | **Received:** 01.05.2022 | **Accepted:** 05.06.2022 | **Published:** 09.06.2022

***Corresponding author:** Houba Abdelhafid
Department of Critical Care medicine, Military Hospital Of Instruction Mohammed V of Rabat, Faculty of Medicine and Pharmacy of Rabat, University Mohammed V, Rabat, Morocco

Abstract **Original Research Article**

Background*:** Tranexamic acid (TA) is proven to be effective to reduce perioperative bleeding in orthopedic surgery. However, it remains underutilized in daily practice. The objective of this study was to assess the usefulness of TA to mimimise blood loss during TKA in countries like ours where the strategies of reducing blood loss are very limited. ***Methods: 112 patients were included, and randomly divided into two group of 56 patients each. One group received the IV TA while the control group did not received. For those who received TA, intravenously 10mg/kg 20 minutes before tourniquet application, 10 mg/kg 15 minutes before deflation of tourniquet, and 10 mg/kg 3 hours after the second dose dose in each knee. The main outcomes were the volume of intraoperative bleeding, the amount of blood in the drains postoperatively, as well as the level of Hb at 24 postoperative hours and 5 day postoperatively, the frequency of transfusion, and the number of red blood cells transfused. Also, all complications were recorded. ***Results*:** There were no statistical differences in demographics data between the groups**.** Mean intraoperative blood loss was significantly lower for TA group than for the control group (124,1±22,2 ml vs 256,4±41,08 ml ; p<0,001). Similarly, the mean amount of blood in the drains postoperatively was lower in TA group than the control group. Thereby, total blood loss was consequently less in TA+ group compared to the control group (1091,5±103,4 ml vs 636,67±48,5 ml ; p<0,001). Postoperative hemoglobin levels were higher for TA group than for the control group at 24 hours and 5 day postoperatively. In the control group 11(19,64%) patients needed blood transfusions, in comparison to only 1(1,78%) patient in the tranexamic acid group (p<0,043). Patients in the tranexamic acid group were given 2 (3,57%) units of red blood packed in total, compared with 21(37,5%) units in the control group. No thromboembolic complication were detected in both groups. ***Conclusion*:** Shortage of blood products and limits of using other techniques minimising blood loss, encourage the use of tranexamic acid, as a better alternative pharmacological to decrease perioperative bleeding during TKA, given its effectiveness, safety and low cost.

Keywords: Total knee arthroplasty, bleeding, transfusion, anesthesia, antifibrinolytic, tranexamic acid.

INTRODUCTION

Total knee arthroplasty (TKA) is the most frequent orthopedic surgery and is associated with a high risk of blood loss intraoperatively, but also in the first postoperative days [1-3]. This type of surgery mandate strategies to reduce blood loss and the need for blood transfusion. One such strategie is using antifibrinolytics agents including aprotinin and tranexamic acid (TA) [4, 5]. Aprotinin is an expensive drug and can induce anaphylaxis [6]. Furthermore, blood products are sometimes scarce and associated with appreciable expense. Thus, TA could be a better alternative especially in countries like ours where the techniques to reduce blood loss are very limited.

TA is a synthetic fibrinolytic inhibitor that competitively inhibits the activation of plasminogen to plasmin ; at high concentrations it non-competitively blocks plasmin, thus TA inhibits the dissolution and degradation of fibrin clots by plasmin [7]. There is no consensus about the starting time, methods, or volume of usage of TA [8, 9]. Multiple doses or topical use combined with IV administration is claimed to be more successful than single-dose usage [10, 11]. Maniar *et al*., [12] compared groups that underwent intravenous

injection of tranexamic acid preoperatively, intraoperatively, and 1-3 times postoperatively and the group that received a single local injection. Their finding was that the three-dose regimens, preoperative, intraoperative and postoperative (POIOPO) produced maximum effective reduction of drain loss and total blood loss than two injections or a local injection.

Therefore, the primary objectives of this present study were to explain efficacy of TA on reducing perioperative blood loss and the number of units of packed red blood cells (PRBC) transfused during total knee arthroplasty TKA. We also examined whether the incidence of postoperative deep venous thrombosis (DVT).

MATERIALS AND METHODS

Inclusion and exclusion criteria

This was a prospective randomised case control study. It was conducted in the operating room of the Military Hospital Mohammed V of Rabat. Between February 2014 and April 2015, all patients scheduled to undergo primary unilateral TKA were eligible to participate in the study. Before the study, the institutional ethical committee approved the study and patients signed informed consent forms. Patients with history of haematological disease, severe cardiorespiratory disease, thromboembolic disease, revision TKA, history of cerebrovascular disorders, renal and hepatic diseases, use of anticoagulants or contraceptive pills 5 days before surgery, anemia (hemoglobin [Hb] <12 g/ dL for men and <11 g/dL for women), abnormal prothrombin time, and abnormal patelet counts were excluded.

The patients were randomized into two groups by an envelope method. The randomization and preparation of the drug were done in the absence of other personnel by 2 anesthesia nurses not engaged in the study.

Anesthetic and surgical procedures

All surgeries were done by the same team of senior surgeons. The pneumatic tourniquet was applied at proximal thigh in whole course until wound closure. Tourniquet pressure was set in accordance with the systolic blood pressure. Midline skin incision and medial parapatellar approach were adopted in all cases, in which the posterior stabilized cemented prosthesis (NexGen LPS; Zimmer Inc, Warsaw, IN, USA) without patellar resurfacing was applied. An intraarticular drain was inserted then removed routinely 36 hours after surgery.

All patients were evaluated by an anaesthesiologist one month before surgery. Antiplatelet agents were interrupted three days before surgery. Patient's premedication included Hydroxyzin 1 mg/kg administered orally a night prior and day of surgery in the morning. In the operating room, intraoperative monitoring including electrocardiography (ECG), noninvasive blood pressure (NIBP), pulse oxymetry, capnography, and urine output was performed in all patients. Intravenouss access was acheived with 16-18G catheter. All patients were preloaded with normal saline (0,9 %) 500 ml prior to anesthesia. Prophylactic treatment with 2 g cefazolin was initiated 30 min before the operation and continued for 24 h as 1 g administered 3 times/day. The choice of the anesthetic technique was left to the discretion of the anesthesiologist. For spinal anesthesia, an injection of 12,5-15mg of hyperbaric bupivacaine mixed with 25 µg of fentanyl was administered after a net reflux of the cerebrspinal fluid by puncturing the L3L4 or L4L5 interspace and the anesthetic levels were tested before the start of the surgery. For general anesthesia, it was induced by fentanyl 2-5mcg/kg, propofol 2-3mg/kg and rocuronium 0,1 mg/kg. Anesthesia was maintained with 1%-2% isoflurane with 50% nitrous oxid in oxygen. Shortly after anesthesia, patients in the TA group received tranexamic acid (Exacyl, Sanofi-Aventis, Casablanca, Maroc ; 500 mg/5 ml) intravenously 10mg/kg body weight mixed in 100 ml normal saline (0,9%) 20 minutes before tourniquet application as a preoperative dose, 10 mg/kg 15 minutes before deflation of the tourniquet as an intraoperative dose, and 10 mg/kg 3 hours after the second dose as a postoperative dose. This regime was based on successful outcomes in literature. If mean arterial pressure decreased to <50 mmHg, then 3 to 6 mg of ephedrine was injected intravenously (IV). For postoperative pain relief injection diclofenac, titration morfine and a continuous sciatic nerve block with a femoral catheter for 72 hours were used according to the requirement of the patient. Thromboprophylaxis was performed using low molecular-weight heparin (enoxaparin 40 mg daily) which was administered subcutaneously for 2 weeks. Patients were examined daily until discharge. If a thromboembolic event was suspected Doppler ultrasound was performed. Rehabilitation was started after drainage tube removal.

Blood transfusion protocol

The cut-offs used to perform blood transfusion were those recommended by the French Healthcare Product Safety Agency in 2002:

- 7 g/dL of Hb in patients free of cardiovascular disease ;
- 8 to 9 g/dL of Hb in patients with established cardiovascular disease (coronary artery disease, cerebrovascular events, peripheral vascular disease, or heart failure) ;
- 10 g/dL of Hb in patients with poor clinical tolerance of lower values.

Data Collection

For all patients, we collected demographic's data (age and gender), as well as general health information (body mass index [BMI] and American

Society of Anesthesiologists [ASA] physical status score). Preoperative Hb, and preoperative antiplatelet agents were also collected. Tourniquet time, duration of surgery, surgical side, anesthetic technique were recorded for every patient.

The volume of blood lost intraoperatively was calculated from the volume of blood in the aspirator and irrigation fluid, plus the volume of blood on the gauze pad (calculated by weighing the gauze pads). Total blood loss was estimated using Mercuriali's formula [11]. This formula is based on the preoperative haematocrit (Hct preop) and fifth post-operative day haematocrit (Hct day 5 postop). The haematocrits must be written as decimal fractions. This formula requires the patient's blood volume (BV) calculated through the Nadler formula [14] (in millilitres of blood) and requires the volume of red blood cells (RBC) transfused as well. Therefore, this estimation using the Mercuriali formula is expressed in millilitres of RBC.

Estimated blood loss= blood volume x (Hct preop - Hct day 5 postoperative) + ml of transfused RBC

The volume of RBC transfused is based on the number of RBC in one blood unit pack. This number is different from one institution to another.

The main outcomes of the current study were the volume of intraoperative bleeding, the amount of blood accumulated in the drains postoperatively until 3 days after surgery, as well as the level of Hb at 24 postoperative hours and day three postoperatively, the frequency of transfusion and the number of packed red blood cells transfused during the intraoperative and postoperative period up to postoperative day 3. Also, patients were evaluated clinically for side effects of TA therapy (thromboembolic events, coronary artery events, seizures, vascular events), which were recorded in each group.

Statistical Analysis

We carried out statistical analysis using Statistical Package for Social Sciences (SPSS) Version 18 (IBM, Chicago, IL, USA). The Kolmogorov-Smirnov test (KS) was used to test for normality. If the data complied had a normal distribution, the results were expressed in the form of mean ± standard deviation (SD). For data with nonnormal distribution, median and 25th and 75th percentiles were used. A two-tailed unpaired t test or Mann-Whitney U test for non-parametric data was used to assess differences in continuous variables. Chi-square test was used to analyze group differences for categorical variables. The P value of <0.05 was considered statistically significant.

RESULTS

Baseline data and clinical characteristics :

A total of 112 primary unilateral total knee arthroplasty (TKA) patients were successfully reviewed. Study patients were divided into 2 group of 56 patients each. One group received the intravenous tranexamic acid (TA group) while the control group did not received. Basic subject, medical characteristics, and data surgery are summarized in Table 1. All demographic characteristics were similar in the two groups. Mean patient age was 57,2±13,2 years in the TA- group and 60,9±14,5 years in the TA+ group. The male-to-female ratio was between 0,69 and 0,86. Preoperative risk according to the ASA class was without significant differences between the two groups. No significant differences were found in the number of preoperative antiplatelet agents, anesthetic technique, operated side, total operative time or using pneumatic tourniquet time. The distribution of operated side was homogeneous in the two groups : the right side (58%) and the left side (42%) in the TA- group, the right side (60%) and the left side (40%) in the group TA+. General anaesthesia was used in 17 (30,3%) of the TA- patients and 14 (25%) of the TA+ patients and spinal anaesthesia in 42 (75%) TA- patients and 39 (69,6%) TA+ patient. Mean operative time was 2,34 ± 0,24 hours in the TA- group and 2,38 ± 0,22 hours in the TA+ group. Nevertheless, no patient in both groups received anticoagulants preoperatively.

Evaluation of blood losses (Table 2)

The volume of intraoperative blood loss was significantly reduced in the TA group (124,1±22,2) compared to the control group (256,4±41,08) with a statistically significant difference (p<0.001). The drainage volume assessed on the 1st postoperative day, 2nd postoperative day was 283,3±23,4 ml, 87,5±25,6 ml, respectively, in group TA+ and 432,8±42,9 ml, 115,3±33,2 ml, respectively, in group control. The combined total drainage volume until the 2d postoperative day was significantly smaller in group TA acid. Total volume of blood losses estimated using Mercuriali's formula were lower in the TA+ group compared to the TA- group. The average blood losse was 1091,5±103,4 in TA- group versus 636,67±48,5 in group TA+. The difference observed between the two groups was significant (p<0.001).

Changes in Hemoglobine levels between preoperative period, at 24 hours and day 5 postoperatively (Table 3)

The hemoglobin level preoperatively was similar (p=0.79) in the two groups, but it was greater in the tranexamic acid group than in the control group at 24 hours and 5 days postoperatively at statistically significant levels (Table 3). The average post-operative 24 h and 5 days Hb was respectively 12,94±0,83 g/dl, 13,06±0,97g/dl in tranexamic group, 11,03±0,86g/dl, 11,38±1,15 g/dl in the control group (Figure 1).

Management of blood losses (Table 3)

Blood transfusion requirement was significantly less in the TA group compared to the control group. The number of patients required blood transfusion was 11 (19,64%) in TA- group, whereas

only 1 (1,78%) patient in the group TA+ required blood transfusion. Patients in the tranexamic acid group were given 2 (3,57%) units of blood in total, compared with 21(37,5%) units in the control group (p<0,001).

Table 1: Demographic, clinical characteristics and data surgery of the study sample

Parameter	Group TA- (n=56)	Group TA+ (n=56)	P value
Age* (years)	57,2 ± 13,2	60,9 ± 14,5	0,27
Gender (M/F), n	26 / 30	23/ 33	0,24
BMI* (Kg/m2)	24,89 ± 3,1	25,09 ± 2,8	0,27
ASA I/II, n	26 / 30	31 / 25	0,23
Preoperative antiplatelet agents, n	09	11	0,78
Operated side R/L, n	27/29	24/32	0,79
Spinal anesthesia/GA, n	39/17	42 /14	0,26
Operative time* (min)	2,38 ± 0,22	2,34 ± 0,24	0,13
Time using tourniquet* (hours)	1,93±0,33	1,82±0,34	0,17

*Data expressed as mean±standard deviation. BMI= body mass index, R=right, L=left, GA=general anesthesia,, ASA=American Society of Anesthesiologists.

Table 2: Blood loss in the tranexamic acid and control groups

Parameter	Group TXA- (n=56)	Group TXA+ (n=56)	P value
Intraoperative blood loss (ml)	256,4±41,08	124,1±22,2	<0,001
Total drainage volume of blood (ml)			
Day 1	432,8±42,9	283,3±23,4	0,036
Day 2	115,3±33,2	87,5±25,6	<0,001
Total Blood loss estimated (ml)	1091,5±103,4	636,67±48,5	<0,001

Values are given as mean±standard deviation.

Table 3: Mean change in haemoglobin levels pre and post surgery, and blood transfusion data in tranexamic acid and control groups

Parameter	Group TXA- (n=56)	Group TXA+ (n=56)	P value
Preoperative Hb[¶] (g/dl)	13,86[13,42-14,2]	14,1[13,6-14,45]	0,71
Hb Day 1 postoperatively[*] (g/dl)	11,03±0,86	12,94±0,83	<0,001
Hb Day 5 postoperatively[*] (g/dl)	11,38±1,15	13,06±0,97	<0,001
Blood transfusion requirements	11(19,64)	1(1,78)	0,043
Units of RBC transfused	21(37,5)	2(3,57)	<0,001

Data given as median (interquartile range), [*] Data expressed as mean±standard deviation. Data are presented as n (%) for categorical variables. Hb=Haemoglobin, RBC=red blood cells.

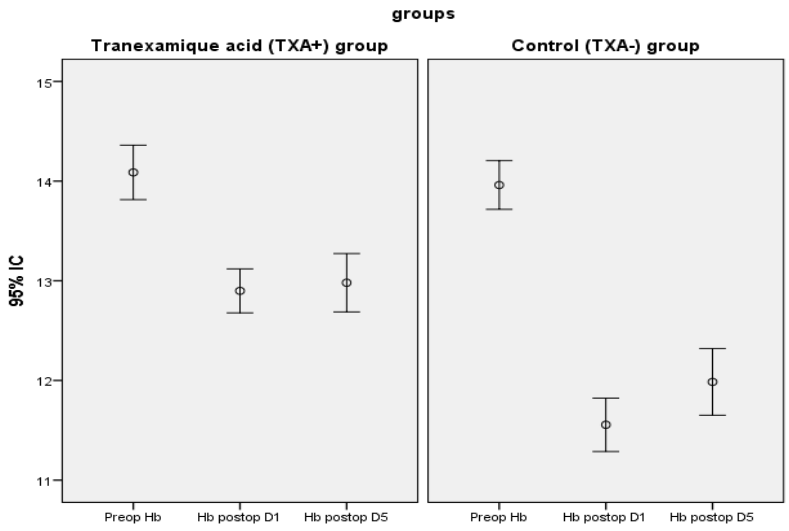

Figure 1: Change in Haemoglobin levels pre and postoperatively in tranexamic acid and control groups undergoing total knee arthroplasty

DISCUSSION

Total knee arthroplasty (TKA) may cause significant perioperative blood loss ranging from 800 to 1800 mL, and 10 to 38% of patients need allogeneic blood transfusion [2, 3, 13]. The use of tranexamic acid (TA) in primary TKA is today widely accepted, and several studies and meta-analyses have confirmed the efficacy of TA at decreasing blood loss without increasing complications and costs. Several clinical trials have identified that intravenous (IV) TA is effective in reducing perioperative blood loss and the need for subsequent blood transfusions in TKA [14, 15]. Pharmacologicaly, intravenous (IV) TA diffuses rapidly into joint fluid and the synovial membrane. Drug concentration and elimination half-life in joint fluid are equivalent to those in serum. Elimination of TA occurs by glomerular filtration, with about 30% of a 10-mg/kg dose removed in 1 hour, 55% over the first 3 hours, and 90% within 24 hours of IV administration [16].

There are different administration route of TA for TKA and all of those have been identified efficient and have not reach consistent. The use of intravenous TA presents satisfactory results shown consistently on the literature, both when given as a single dose and when adding a second or third dose intraoperatively or postoperatively. Levine *et al*., [17] in a randomized controlled trial, demonstrated that a standard dose of 1 g IV can be used with the same efficacy as weighted doses (20 mg/kg). However, Iwai *et al*., [18] demonstrated that a double IV dose of TA produced a further reduction of postoperative blood loss in TKA compared to a single administration, especially if the doses were given preoperatively and intraoperatively. Morever, Maniar *et al*., [12] showed in their study that the three-dose regimen of preoperative, intraoperative and postoperative (POIOPO) produced maximum effective reduction of drain loss and total blood loss. In line with these results, we used three-dose scheduled regimen with a preoperative dose, a second doseintraoperative procedure followed by 3 h after the second dose as a postoperative dose.

According to the results of this study, TA group showed the ability to reduce intraoperative blood loss compared to the control group, which did not receive TA (124,1±22,2 ml vs 256,4±41,08 ml ; p<0,001). The mean amount of blood in the drains postoperatively was also lower in the tranexamic acid group than the control group (p<0,05). Thereby, total blood loss estimated was consequently less in the TA group than the blood loss in the control group (1091,5±103,4 ml vs 636,67±48,5 ml ; p<0,001) which is in accordance with the volumes stated in the literature.

To reduce the potential risk of thromboembolic complications and extended the effect of TA postoperatively, the topical administration TA including intra-articular and infusion TA was evaluated in previous studies and with notable clinical relevant effect compared with intravenous.

There was also significant difference in the postoperative hemoglobin values of patients in the TA group compared to the control group. Postoperative anemia correlates with decreased ambulation ablity and performance during the early postoperative period [19]. In general, higher postoperative hemoglobin levels result in improved motor performance and shorter recovery [20].

When compared to TA group, proportion of the patients requiring blood transfusion was significantly more higher to 19,64% in control group. Patients in the tranexamic acid group were given 2 (3,57%) units of blood in total, compared with 21 (37,5%) units in the control group. Transfusions impede physical therapy. Stokes *et al*., [21] found the disadvantages of blood transfusion after total knee and hip arthroplasty include longer length of hospital stay, infection, increased morbidity and mortality, especially in increased costs. Therefore, it is a great challenge for practitioners to reduce blood loss in total knee arthroplasty.

It is also important to understand that increased thromboembolic complications might nullify cost versus benefits. Most important concerns for initiation of this protocol was the antifibrinolytic effect of TA, which might lead to an increase in venous thromboembolic events. However, literature regarding this suggests TA does not result in an increase in thromboembolic events. Cid *et al*., [14, 22] have shown that the use of TA was not associated with an increase in thrombotic complications either clinically or anywhere documented radiologically. No patients in our study experienced a complication from the use of TA.

Although our study is prospective, it has certain limitations. As this was based on patient population at a single institution, the results may not be generalizable to an entire population. Additionally, we looked for the side effects of tranexamic acid only up to two weeks when the patient reported for suture removal. Any potential complications that could have presented later have not been accounted.

CONCLUSION

The shortage of blood products, the limits of using other techniques minimising blood loss and other antifibrinolytics agents, encourage the use of tranexamic acid, as a better alternative pharmacological to decrease perioperative bleeding during total knee arthroplasty, given its effectiveness, safety and low cost.

ACKNOWLEDGMENTS

The authors thank the team of Department of Anesthesiology and critical care Medicine at Military Instruction Hospital Mohammed V of Rabat for providing support and helping in the preparation of the manuscript

Conflicts of Interest : All authors disclose that there was no conflict of interest.

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