Tranexamic Acid to Reduce Blood Loss After Bilateral Total Knee Arthroplasty

A Prospective, Randomized Double Blind Study

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Abstract: The effects of 2-dosage regimens of tranexamic acid (10 mg/kg and 15 mg/kg) on blood loss and transfusion requirement were compared to saline placebo in 60 patients undergoing concurrent bilateral total knee arthroplasty, with additional reinfusion autotransfusion from intraarticular drains. Mean blood loss was 462 mL in 15 mL/kg group, 678 mL in 10 mg/kg group, and 918 mL in controls ($P < .01$ vs 15 mg/kg). Blood available for autotransfusion was greatest in controls and least in 15 mg/kg group. Combined autologous and allogenic transfusion volumes were similar in the treatment groups and significantly less than controls ($P < .01$). With use of an autologous reinfusion strategy, the lower dose is sufficient to lead to a lesser allogenic transfusion requirement. **Keywords:** bilateral total knee arthroplasty, blood loss, transfusion, tranexamic acid.

Tranexamic acid (TA) is a synthetic amino acid that inhibits fibrinolysis by reversible blockade of lysine binding sites on plasminogen molecules, inhibiting its activation. This prevents plasmin from binding with fibrinogen and fibrin structures after clot formation [1]. At higher concentrations, TA may be a direct noncompetitive inhibitor of plasmin. With intravenous administration, maximum plasma levels are found at 5 to 15 minutes; it diffuses rapidly into the synovial fluid and membrane, with therapeutic levels maintained for approximately 3 hours [2].

Two recent meta-analyses have been performed to evaluate the effect of intravenous TA in reduction of blood loss and transfusion requirement in total hip arthroplasty and total knee arthroplasty (TKA) [3,4]. From clinical trials considered suitable for evaluation, it was concluded that TA appears effective and safe in reducing allogenic blood transfusion and blood loss, without increasing thromboembolic complications, while seeming cost-effective.

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However, there was considerable variability in timing of administration and in dosage of TA among these studies, as well as in rates of transfusion [5-9]. The regimen of 2 intravenous boluses (10-15 mg/kg), the first given before tourniquet deflation or skin incision and the second, 3 hours later, was used most frequently. It was noted that there was little literature about TA in revision arthroplasty where blood loss and transfusion rates are likely to be higher. Concurrent bilateral TKA would also be expected to be associated with a higher transfusion requirement, and as far as can be ascertained, there have been no controlled studies or publications on this group of patients.

In this prospective, randomized double blind study, we evaluated the effect of 2 different dosage regimens of TA vs placebo on blood loss and allogenic transfusion requirements in patients undergoing concurrent bilateral TKA.

Patients and Methods

Following approval from the institutional ethics and research committee, written consent was obtained from 60 patients presenting for concurrent bilateral TKA. The patients were randomly allocated to 1 of 3 groups as follows:

- group 1 received 2 doses of TA of 10 mg/kg,
- group 2 received 2 doses of TA of 15 mg/kg, or
- group 3 received 2 equal volumes of normal saline (the control group).

Table 1. Patient Demographics

Group	Control	TA 10 mg/kg	TA 15 mg/kg	Significance
Patients	20	20	20	
Sex (male-female)	5:15	7-13	8-12	NS
Age, y	66 (±7.3)	62 (±4.3)	65 (±4.3)	NS
Weight, kg	73 (±16.6)	79 (±17.3)	74 (±4.3)	NS
Height, cm	153 (±5.9)	155 (±7.0)	157 (±7.7)	NS
ASA score	2	2	2	

Values expressed as means ± SD. NS indicates not significant; ASA, American Society of Anesthesiologists.

Patients were not eligible for inclusion in this study if they had a known allergy to TA, a history of hepatic or renal dysfunction, severe cardiac or respiratory disease (myocardial infarction within 6 months, unstable angina, aortic or mitral valvular stenosis), previous stroke, congenital or acquired coagulopathy, or history of thromboembolic disease.

Anesthesia technique was standardized to propofol target controlled infusion with remifentanil total intravenous anesthesia, controlled ventilation, and placement of an epidural catheter for postoperative analgesia. All surgery was performed by the same orthopedic surgeon, using a surgical technique standardized to the same design cemented knee prostheses (NexGen, Zimmer, Warsaw, Ind), under pneumatic tourniquet, with placement of an intraarticular drain for reinfusion autotransfusion (Hemovac, Zimmer) at the conclusion of surgery. The right leg was operated on first in all patients.

Tranexamic acid (Cyklokapron, 100 mg/mL; Pharmacia, Uppsala, Sweden) or placebo (physiologic saline) for infusion was prepared by the institution's pharmacy in 2 identical 50-mL bags (identified only by random number), with the constituents unknown to the administering anesthesiologist or surgeon. Patients received the first infusion over 10 minutes before deflation of the first tourniquet and the second (also over 10 minutes) 3 hours after the first.

Preoperative investigations included hemoglobin (Hb) level, hematocrit, platelet count, prothrombin index (PI), international normalized ratio (INR), and activated partial thromboplastin time (aPTT). Volumes of crystalloid (normal saline or Lactated Ringer solution) and colloid (Voluven, Fresenius, Bad Homburg, Germany) infused were recorded. At the conclusion of surgery, the volumes collected by the intraarticular drains were recorded, with retransfusion of autologous blood according to a standard protocol (Appendix A). Further drainage volumes were recorded until removal of the drains on the first postoperative day. Postoperative Hb level, hematocrit, platelets, PI, INR, and aPTT were tested after 6 hours and on the first and third postoperative days.

Postoperative Hb values less than 80 g/dL after autologous retransfusion prompted transfusion of allogenic packed red blood cells (PRBC); all such transfusions were recorded. Prophylaxis with oral warfarin, 2.5 to 5 mg (coumadin), for thromboembolic complications was administered daily. Any thromboembolic or other complications occurring during the hospital stay were recorded.

It was calculated that a sample size of 20 in each group would have a 90% power to detect a difference in mean blood loss of 300 mL (assuming an SD of 280) using a 2-group *t* test with a 0.050 2-sided significance level. Data are expressed as mean (SD), with 1-way analysis of variance and a Bonferroni correction of the *P* value for the differences between the groups.

Results

Details of the patients in the 3 groups are shown in Table 1; there were no significant differences between them as far as the data presented. The duration of surgery and tourniquet times was comparable in all groups (Table 2).

Total blood loss measured from the drains was greater in the control group (918 ± 549 mL) than in either the 10 mg/kg (678 ± 331 mL) or 15 mg/kg (462 ± 209 mL) TA groups, though only achieving significance between control and 15 mg/kg ($P < .01$) (Table 3). The losses for the right leg were 306 (±153) mL in the treatment groups and 525 (±334) mL for controls and 263 (±156) mL vs 393 (±275) mL for the left leg. There were no significant differences in blood loss between men and woman in the 3 groups.

In the immediate postoperative period (0-4 hours), blood loss from the Hemovac drains in the control group was greater than in either of the TA groups. Hence, blood available for autotransfusion was significantly higher in the control group (17/20 patients received 596 ± 493 mL) than in the 10 mg/kg group (11/20 patients received 245 ± 262 mL; $P < .05$) and in the 15 mg/kg group (6/20 patients received 86 ± 150 mL; $P < .01$) (Table 3).

Allogenic transfusion requirement was higher in the control group (10/20 patients receiving 19 U PRBC) and in the 15 mg/kg group (9/20 patients receiving 18 U

Table 2. Surgical Demographics

Group	Control	TA 10 mg/kg	TA 15 mg/kg	Significance
Patients	20	20	20	
Right leg				
Surgery, min	98 (±22.5)	96 (±20.1)	89 (±20.0)	NS
Tourniquet	106 (±19.7)	106 (±20.1)	100 (±20.0)	NS
Left leg				
Surgery, min	99 (±13.8)	94 (±36.0)	99 (±15.7)	NS
Tourniquet	105 (±13.6)	98 (±21.9)	104 (±14,5)	NS
Fluids				
Crystalloid	2197 (±397)	2055 (±336)	2100 (±475)	NS
Colloid	434 (±261)	372 (±460)	460 (±305)	NS

Values expressed as means ± SD. NS indicates not significant.

Table 3. Blood Loss From Drains and Transfusion

Group	Control	TA 10 mg/kg	Significance	TA 15 mg/kg	Significance
Patients	20	20		20	
Blood loss, mL	918 (±549)	678 (±331)	NS	462 (±209)	<.01
Autotrans, mL	596 (±493)	245 (±262)	<.05	86 (±150)	<.01
Allogenic, mL	332 (±290)	140 (±197)	NS	315 (±223)	NS
Combined, mL	928 (±569)	385 (±241)	<.01	401 (±186)	<.01
Patients transfused	10	4		9	NS
PRBC units	19	8		18	NS

Values expressed as means ± SD. Significance indicates *P* value vs control.

PRBC) than in the 10 mg/kg group (4/20 patients receiving 8 U PRBC), without achieving statistical significance. Allogenic transfusion was required earlier in the control group (on day 2 as against day 3 or 4), despite autologous transfusion from the drains.

Given that a unit of PRBC from the hospital's blood bank has a volume of 350 mL (±70 mL), when the volumes of autologous and allogenic transfusion were combined, there was no difference between the 10 mg/kg (385 mL) and 15 mg/kg (401 mL) groups but with a significant difference to the control group (928 mL; $P < .01$) (Table 3). Blood loss and transfusion rates were not significantly different in patients with a low starting Hb value (<120 g/dL) in the control and 10 mg/kg group but were higher in the 15 mg/kg group ($P < .01$) (Table 4).

Preoperative Hb level, hematocrit, platelets, PI, INR, and aPTT values were similar among the 3 groups, without significant difference in mean values between men and women. While compared to preoperative values, Hb concentration decreased progressively at each assessment, and there was no difference between groups (Table 5). There were no significant differences in coagulation factors.

Two patients, one from the 10 mg/kg and one from the 15 mg/kg groups, developed non–life-threatening pulmonary embolus diagnosed by spiral computerized tomography after an episode of chest pain.

Discussion

Total joint arthroplasty is associated with significant perioperative blood loss. There is considerable variation in the magnitude of reported loss; for single TKA without antifibrinolytics, the average range is from 761 mL to 1784 mL [5-11]. Although surgical technique may account for some of this variability, most studies estimated loss by measured collection from the drains [5-9]. It is recognized that blood collected in the intraarticular drains will not be an accurate reflection of total blood loss, due to covert accumulation in the tissues. Hence, a more accurate estimation of total blood loss may be obtained by including calculation of covert loss as derived from serial changes in Hb or hematocrit levels [10,11].

Various strategies have been used in an attempt to reduce this loss. These have included a lower transfusion trigger; autologous predonation with or without erythropoietin; intraoperative and postoperative red cell salvage; and the antifibrinolytic agents aprotinin, e-aminocaproic acid, and TA [12]. Of these, intravenous TA is less expensive and less allergenic than aprotinin and up to 10 times more potent than e-aminocaproic acid.

Most of the external blood loss occurs in the first few hours postoperatively after removal of the tourniquet(s), when the TA would be most effective. In one study that calculated covert loss, TA was effective in reducing measured loss but did not significantly reduce the hidden loss [10], which may explain why there is still a requirement for allogenic transfusion, albeit diminished. The proportion of patients requiring allogenic transfusion after TA has been shown to be less than that in controls (68%) [3,4].

In this study, we have shown that both doses of intravenous TA were effective in reducing immediate postoperative blood loss as measured from the drains; however, this was only significant with the higher dosage of 15 mg/kg. Blood collected in the drains in the

Table 4. Preoperative Hb Values and Transfusion Volumes

Group	Hb level, <120 g/dL	Hb level, >120 g/dL	Significance
Controls	1152 (±423)	878 (±709)	NS
n	4	16	
TA 10	355	388 (±357)	NS
n	2	18	
TA 15	718 (±265)	322 (±230)	<0.01
n	4	16	

Values expressed as means ± SD. n indicates number of patients; significance, *P* value difference between means.

Table 5. Hemoglobin level (g/dL)

Group	Control	TA 10 mg/kg	TA 15 mg/kg	Significance
Patients	20	20	20	
Preoperative	129 (±12.4)	135 (±13.2)	130 (±15.9)	NS
6 h postoperative	107 (±11.7)	116 (±13.4)	111 (±17.9)	NS
Day 1	95 (±13.0)	108 (±13.7)	105 (±15.2)	NS
Day 3	93 (±8.2)	95 (±31.2)	102 (±9.2)	NS

Values expressed as means ± SD. NS indicates not significant.

first 4 hours was given as an autologous transfusion according to protocol. As the 15 mg/kg TA dosage was effective in reducing blood loss, there was consequently less available for reinfusion in this group. This may also explain why it was only in this group that there was a correlation between preoperative Hb values and transfusion volumes (Table 4) because allogenic blood was required later in the postoperative course.

Given that perioperative fluid replacement, crystalloid, and colloid were not significantly different between the groups, the change in Hb values can also be used as a marker of blood loss. Hemoglobin levels fell in all 3 groups progressively through the study period, despite the reinfusion of autologous blood from the drains. The fall in Hb level was greatest in the controls and similar in the TA groups. In the 10 mg/kg group, there was more autologous transfusion on the first day and less requirement for subsequent allogenic blood. In the 15 mg/kg group, there was less immediate drainage available for autotransfusion; however, by the third or fourth postoperative day in almost half the patients, Hb values had fallen to the trigger level (80 g/dL), prompting transfusion of allogenic blood.

Although the higher dose of TA led to less immediate postoperative blood loss, as a strategy that included autologous collection and reinfusion was used, this did not produce the desired effect of reducing allogenic transfusion in this group. In fact, the lower TA dose was more effective in this regard. When both autologous and allogenic transfusion volumes were combined, there was no difference between the TA groups, but there was a significant difference to the controls.

Compared to previous studies on the effect of TA on blood loss and transfusion requirement in TKA [5-10], considering that all these studies were on single TKA, the amount of blood loss in this study on concurrent bilateral TKA was surprisingly low (Table 6). Surgical technique involving the subvastus approach may have contributed to this finding [13,14]. It is possible had the total measured blood loss in the control patients been higher that TA would have demonstrated a greater effect.

Unlike most other studies on the effects of TA [5,6,8-10], prophylaxis for thromboembolic complications was with oral anticoagulant (warfarin) rather than low-molecular-weight heparin. There were 2 documented instances of pulmonary embolus (PE) in this study, an incidence of 3.3%. The meta-analysis had a combined incidence of deep venous thrombosis (DVT) of 5% in the TA treatment patients and 5.5% in controls, leading to the conclusion that there was no increase in risk of thromboembolism with TA in patients without a history of thromboembolic disease [3]. Incidence of PE was not given. In 2 individual studies, documented PE was seen in 1/13 in one control group [4] and 1/43 in another, also in the control group [5]; in five other studies, there was a zero incidence given [6-10].

A recent retrospective review of bilateral TKA compared incidences of symptomatic PE in simultaneous and staged procedures [15]. A pulmonary embolism developed in 0.81% of patients who had a single procedure and 1.44% of patients who had undergone a simultaneous procedure. The conclusion was that the sum of the risks associated with the 2 operations of a staged procedure may exceed the risk of simultaneous bilateral TKA. The actual incidence of asymptomatic DVT and PE may be much higher. A study using radionuclide venography found an incidence of DVT of 24% and PE of 12%; all patients were asymptomatic [16]. The National Institutes of Health Consensus Development Program found that detection and treatment of asymptomatic DVT does not alter the occurrence of symptomatic DVT or PE after TKA and that the use of warfarin does not protect against symptomatic DVT or PE, compared to no anticoagulation [17]. Perhaps the encouraging early reports of the use of the oral direct thrombin inhibitor dabigatran etixalate may lead to improved thromboprophylaxis for these patients [18].

Table 6. Blood Loss After TKA: Comparison Between Intravenous TA and Placebo

	Treatment		Control		
Study	Patients	Loss (SD)	Patients	Loss (SD)	Significance
Unilateral					
Hippala (1995)	15	847 (356)	13	1549 (574)	<.001
Benoni (1996)	43	730 (280)	43	1410 (480)	<.001
Jansen (1999)	21	678 (352)	21	1419 (607)	<.001
Tanaka (2001)	73	699 (178)	26	1470 (251)	<.01
Veien (2002)	15	409 (175)	16	761 (313)	<.001
Good (2003)	27	385	24	845	<.001
Camarasa (2006)	35	798 (406)	60	1270 (625)	<.001
Bilateral					
MacGillivray (2004)	40	569 (294)	20	918 (549)	<.01

Values are presented as blood loss (±SD).

Conclusion

Tranexamic acid administration reduces blood loss after bilateral TKA. If a system for reinfusion autotransfusion is used concurrently, a lower dose of TA is sufficient to reduce requirement for allogenic transfusion.

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Appendix A

Postoperative blood collection and reinfusion using the Hemovac autotransfusion system:

1 Setup:

Using sterile technique CPD, 56 mL is added to collection bottle. After wound closure, evacuator tube is connected to drain and then linked to collection bottle.

2 Collection:

Blood collected during first 4 hours, reinfused over next 2 hours.

Maximum volume per collection device, 400 mL

Minimum volume for infusion, 100 mL

If more than 300 mL was collected in 4 hours, second unit may be connected

3 Reinfusion:

In accordance with time limitations of AABB (American Association of Blood Banks) standard: 4 hours

Maximum reinfusion rate at 6 mL/min via 40 μ filter

Reinfusion not under pressure

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