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The Effectiveness of Tranexamic Acid in Total Knee Arthroplasty

Eun Il Soo, Kim Doo Yeol and Kim Jong Min*

Department of Orthopedic Surgery, Good Samsun Hospital, Korea

Abstract

Purpose: To investigate the clinical results of the injection of Tranexamic Acid (TNA) into the articular cavity and/or the insertion of suction drainage, in patients undergoing total knee arthroplasty.

Materials and Methods: 192 patients undergoing total knee arthroplasty for degenerative knee arthritis were assigned randomly to 3 groups: Group 1 (TNA plus suction drainage); Group 2 (TNA only); Group 3 (suction drainage only). The 26 following data were analyzed: total blood loss after operation, hidden blood loss, number of transfusions, and amount of drainage, leg swelling, wounds, and other problems.

Results: The total average blood loss and number of transfusions were significantly lower in Group 2 ($p<0.0001$), and this group experienced no problems with wounds. The average hidden blood loss was greater in Group 2, and leg swelling increased immediately following the surgery, but the swelling diminished within six weeks. There was no significant difference in the range of knee joint motion in the three groups two months after the operation ($p=0.0789$).

Conclusion: It is advisable to inject TNA into the articular cavity during total knee arthroplasty, and not to use suction drainage.

Keywords: Tranexamic acid; Total knee arthroplasty; Total blood loss; Hidden blood loss

Introduction

There is a considerable amount of blood loss with total knee arthroplasty, often requiring blood transfusions, which increases the risk of immunological rejection and disease transmission [1-4]. Blood loss reduction methods include autologous blood transfusions [5], hypotensive anesthesia [6], locking the suction drainage tube [7,8], fibrin tissue attachment [9], compression bandages and cold therapy [10], and Tranexamic Acid (TNA) [11-13]. Among these TNA is the most effective at reducing blood loss and does so via fibrin dissolution inhibition, which separates plasminogen from the fibrin surface by blocking the plasminogen lysine binding [8]. Reports also indicate that intra-articular TNA injections are more effective than intravenous injection [11]. In addition to these methods of reducing blood loss, Suction drainage tubes are also used in total knee arthroplasty to prevent complications from hematomas [14,15]. However, their use is debatable. Previous studies reported that a suction drainage tube did not affect the clinical outcome after surgery and that reducing the transfusion frequency rather than using a suction drainage tube reduced blood transfusion complications [16]. Despite this, most cases use a suction drainage tube out of concerns for infection, edema, and a decreased range of postoperative knee joint movement. This study investigated whether a suction and drainage tube is necessary if TNA is injected into the articular cavity during total knee arthroplasty.

Patients and Methods

Patients

This study was conducted after approval for the study was obtained from the Research Ethics Committee. This prospective study included 192 patients who underwent unilateral total knee arthroplasty for degenerative knee arthritis from August 2019 to April 2020. The patients were randomly divided into three groups (64 patients each): Suction drainage tube with TNA (Shin Poong Pharm Co., Ltd., Ansan, Korea) (Group 1), TNA only (without suction drainage tube) (Group 2), and suction drainage tube without TNA (Group 3). Patients with traumatic arthritis, rheumatoid arthritis, angina, myocardial infarction, cardiovascular diseases (e.g., arrhythmia), cerebrovascular

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Correspondence:
Kim Doo Yeol, Department of Orthopedic Surgery, Good Samsun Hospital, Busan, Korea,
E-mail: genesis9917.jm@gmail.com

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diseases (e.g., stroke), or thromboembolism were excluded. There were no significant differences in patient age, gender ratio, and body mass index, etc. in each group (Table 1).

Methods

All patients underwent total knee arthroplasty by one orthopedic surgeon. During surgery, a tourniquet with 260 mmHg of pressure was used, as well as median skin incision and medial parapatellar approach. Intramedullary guides for the femur and extramedullary guides for the tibia were used for bone resection. The posterior cruciate ligament complimentary replacement (NexGen® LPS; Zimmer Inc, Warsaw, IN, USA) was used without patella replacement, and meticulous electric cauterization was performed for soft tissue bleeding. Three grams of TNA was mixed with 100 mL of saline solution and directly injected into the knee joint after suturing the surgical wound. A suction drainage tube (if used) was placed in the articular cavity and subcutaneously, and suction drainage was performed 2 h after surgery. Blood transfusions were performed based on the National Institutes of Health Consensus Conference blood transfusion guidelines when the hemoglobin value was less than 8.0 g/dL or less than 10.0 g/dL with anemia symptoms. If objective symptoms (e.g., paleness, hypotension, tachycardia, shortness of breath, and confusion of consciousness) and subjective symptoms (e.g., dizziness, headache, and fatigue) occurred, then anemia was assumed, and a transfusion was performed. To monitor lower extremity swelling, the thigh (10 cm above the upper patella), knee (upper patella), and calf (the thickest part) circumferences were measured before surgery and 1-, 2-, 4-, and 6-weeks after surgery. Patients took Rivaroxaban for 14 days to prevent complications, such as Deep Vein Thrombosis (DVT) and pulmonary embolism. Patients with suspicious DVT findings, such as pitting edema and elevated D-dimer, were examined by diagnostic Doppler ultrasound. All postoperative complications were investigated (e.g., infection, superficial wound problems, hematomas, hemorrhagic spots, and erythemas), and the knee range of motion was measured two months postoperatively.

Methods of assessment

Blood loss during surgery, drainage after surgery, and hemoglobin before and after surgery were measured, and the total and hidden blood losses were determined using the following formulas by Good et al. [13]:

$$\text{Total Blood Loss} = 1000 \times Hb_{loss}/Hb_i$$

$$Hb_{loss} = BV \times (Hb_i - Hb_e) \times 0.001 + Hb_t$$

$$\text{Hidden Blood Loss} = \text{Total Blood Loss} - \text{drainage}$$

Hb_{loss}= hemoglobin loss (g); Hb_i= the preoperative hemoglobin concentration (g/L); Hb_e= the postoperative hemoglobin concentration (g/L); Hb_t= hemoglobin gain at the time of transfusion (g) Calculated as 52 for one transfusion; BV = Blood Volume (mL), calculated as the total blood volume using the formula by Nadler et al. [14].

Statistical analysis

Statistical analyses were conducted using SPSS Version 18.0 (SPSS Inc., Chicago, IL, USA). The average total blood loss, hidden blood loss, hemoglobin, platelets, Fibrinogen, PT (Prothrombin Time), D-dimer, and leg swelling among the three groups were analyzed by one-way analysis (ANOVA) of variance. A post-hoc test was performed by Scheffe's method, and repeated t-tests were conducted to assess leg swelling. The mean drainage amounts of Groups 1 and 3 were analyzed by t-test, and the number of transfusions among the three groups was analyzed by chi-square test. Statistical significance was set to P ≤ 0.05.

Results

The average total blood loss was 891 mL in Group 1 (suction drainage tube with TNA), 710 mL in Group 2 (TNA only), and 1391 mL in Group 3 (suction drainage tube without TNA). The TNA groups (Group 1, 2) had markedly less blood loss compared to the group without TNA (Group 3). Between TNA groups (Group 1, 2), Group 2 (TNA only) had significantly less blood loss than Group 1 (Table 2), and there was statistically significant difference (P<0.0001). The average drainage amount was significantly lower in Group 1 (492 mL, with suction drainage tube) compared to Group 3 (939 mL, without suction drainage tube) (Table 2; P<0.0001). The average hidden blood loss was 322 mL in Group 1, 546 mL in Group 2, and 355 mL in Group3; there was significantly more hidden blood loss in the groups using the suction drainage tube (Table 2; P<0.0001). The average hemoglobin difference before and after surgery was 1.69 g/dL in Group 1, 1.49 g/dL in Group 2, and 2.55 g/dL in Group 3 (Table 3) and there was statistically significant difference between day 1 and 3 (P<0.0001). The platelet, fibrinogen, and PT averages before and after surgery were measured (Table 4), and there was no statistically significant difference (p=0.6618, p=0.3750, p=0.0731). The average postoperative D-dimer was significantly lower in the TNA groups compared to the group without TNA (Table 4), and there was statistically significant difference (P<0.0001), which is thought to be due to the antifibrinolytic effect of TNA. Of 64 cases of each group, 5 patients (5/64; 7.8%) of group 1 received a transfusion; three had hemoglobin levels less than 8.0 g/dL, and two had less than 10.0 g/dl with anemia symptoms. 23 patients (23/64; 36%) of group

Table 1: Demographic factors for the 3 treatment groups.

	Group 1	Group 2	Group 3	p-value
Mean Age (years)	69.5	70.9	71.2	NS
Gender: Male/female	6/58	6/58	7/57	NS
Height (cm)	156.81	153.14	157.28	NS
Weight (kg)	64.39	60.76	64.09	NS
Mean BMI (kg/m^2)	26.16	25.9	25.89	NS

BMI: Body Mass Index

Table 2: Blood loss in the 3 treatment groups.

	Group 1	Group 2	Group 3	p-value
Total blood loss (ml)	891	710	1391	<0.0001
Drainage volume (ml)	492		939	<0.0001
Hidden blood loss (ml)	322	546	355	<0.0001

Total blood loss and drainage volume were lower in Groups 1 and 2, which used TNA. They were lowest in Group 2 which did not use a suction drainage tube. Hidden blood loss was highest in Group 2

Table 3: Change of hemoglobin (g/dL) level before and after surgery in the 3 groups.

	Group 1	Group 2	Group 3	p-value
Before operation	12.59	12.39	12.50	0.6001
After operation	11.39	11.50	11.02	0.0481
Postoperative 1 day	10.9	10.9	9.95	<0.0001
Postoperative 2 days	10.3	10.5	8.77	<0.0001
Postoperative 3 days	10.2	10.4	9.21	<0.0001

Hemoglobin levels decreased less in the groups which used TNA, especially Group 2

Table 4: Change of coagulation factors in the 3 treatment groups (values are means).

	Group 1	Group 2	Group 3	p-value
Preoperative platelet (× 10^3/μL)	226.89	230.09	243.52	0.2735
Postoperative platelet (× 10^3/μL)	204.82	209.40	214.20	0.6618
Preoperative fibrinogen (mg/dL)	453.83	420.93	420.22	0.1113
Postoperative fibrinogen (mg/dL)	480.40	447.57	439.26	0.3750
Preoperative PT (INR)	1.04	1.05	1.03	0.5130
Postoperative PT (INR)	1.11	1.11	1.14	0.0731
Postoperative D-dimer (μg/ml)	331	257	418	<0.0001

There was no statistically significant difference among the coagulation factors before and after surgery, except for D-dimer which decreased significantly in Group 2

Table 5: Number of patients requiring transfusions.

	Group 1	Group 2	Group 3	p-value
Hb<8.0 (g/dL)	3	0	23	
8.0<Hb<10.0 (g/dL)	2	0	0	
Total	5/64 (7.8%)	0/64 (0%)	23/64 (36%)	<0.0001

The transfusion frequency was less in the groups which used TNA, especially for Group 2. Hb: hemoglobin

Table 6: ROM of the knee 2 months after surgery for 3 groups.

	Group 1	Group2	Group 3
mean extension-mean flexion for all patients in the group	2.7-126.4	2.5-129.3	2.2-128

There was no significant difference in ROM of the knee among the 3 groups. ROM: Range of Motion

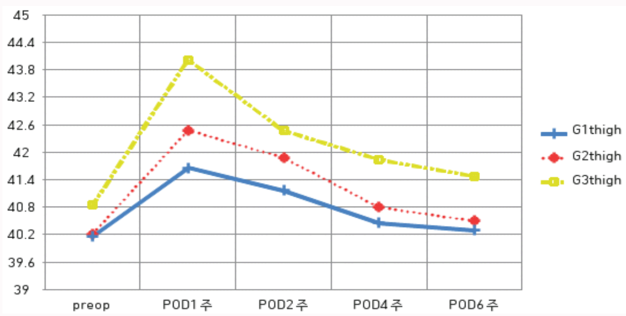

Figure 1: Thigh swelling in the 3 groups before and following surgery. The amount of thigh swelling was small in the groups which use TNA. In Group 2, thigh dimensions were normal by about 6 weeks after the operation.

3 received a transfusion; hemoglobin levels were less than 8.0 g/dL in all patients. There were no transfusions in Group 2 (Table 5), and the transfusion frequency between the groups was significantly different (P<0.0001). The mean differences between the preoperative and 1-week postoperative leg swelling measurements were 1.5 cm (thigh), 1.96 cm (knee), and 1.09 cm (calf) in Group 1, 2.26 cm (thigh), 2.3 cm (knee), and 2.02 cm (calf) in Group 2, and 3.18 cm (thigh), 4.3 cm (knee), 4.1 cm (calf) in Group 3; the measurements among the groups were significantly different (P<0.0001). In the TNA groups, leg swelling was mild. However, in the TNA group without a suction drainage tube (Group 2), leg swelling increased soon after surgery but recovered to a level similar to Group 1 after approximately six weeks (P=0.5595, repeated t-test). Infection and pulmonary embolism did not occur in any group. There were two DVT cases in each TNA group and one in the group without TNA. Ecchymosis and erythema slightly increased in Group 2 but was normal again approximately six weeks after surgery. Superficial wounds did not occur in the TNA groups, but there were two cases in the group without TNA (but the

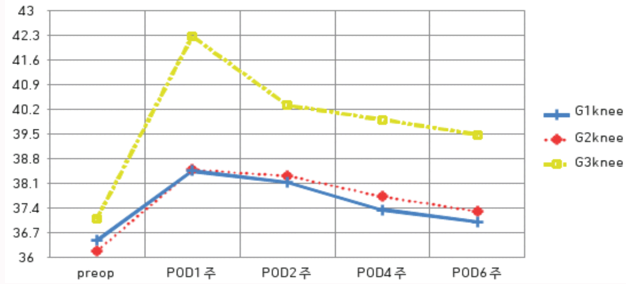

Figure 2: Knee swelling decrease in the weeks following surgery. Knee swelling decreased significantly in the groups which used TNA.

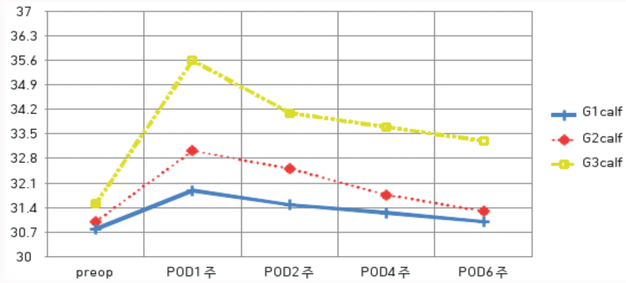

Figure 3: The change in calf swelling in the weeks following surgery. In Group 2, calf swelling increased in the initial period following surgery, but it returned to normal in about 6 weeks.

patients recovered without any complications). The average knee joint ranges of motion two months postoperatively were 2.7-126.4° in Group 1, 2.5-129.3° in Group 2, and 2.2-128.3° in Group 3 (Table 6) with no significant difference among the groups.

Discussion

A large amount of bleeding due to total knee arthroplasty may increase early complications, such as pulmonary embolism, hypovolemic shock, and infection at the surgical site, as well as blood transfusions and subsequent side effects. Previous studies investigated anti-fibrinolytic agents, such as aprotinin, e-aminocaproic acid, and TNA, as a way to reduce bleeding and, thereby, transfusions. TNA, in particular, is relatively inexpensive, causes fewer allergic reactions than aprotinin, and is more effective than e-aminocaproic acid. TNA blocks the plasminogen lysine-binding site, inhibiting plasmin formation (the active form), thereby blocking downstream processes (where plasmin binds to fibrinogen or fibrin structure), and preventing fibrin dissolution [13]. In addition, TNA is rapidly absorbed when injected into the articular cavity, which stops fibrin aggregate dissolution in the surrounding area and creates a partial microvascular hemostasis effect. The biological half-life of TNA is approximately three hours [18] and it accumulates in the surrounding tissues for approximately 17 h [19]. Based on this mechanism, TNA is used in dentistry, cardiac, spine, and hip surgeries, and recently, reports continue to support TNA effectiveness in total knee arthroplasty. Seo et al. [11] reported that intra-articular TNA injections produced better results than intravenous injections in total knee arthroplasty, and Wong et al. [20] found that intra-articular TNA injections reduced total blood loss and the transfusion frequency. A meta-analysis by Panteli et al. [21] reported that a low TNA dose injected into the articular cavity reduced blood loss but not the number of blood transfusions. Conversely, a high TNA dose reduced blood loss and the number of transfusions but did not increase the frequency of thromboembolic complications. Intra-articular injections are safer because TNA is injected directly into the bleeding area, minimizing potential systemic effects compared to intravenous injections. Wong et al. [20] reported that TNA reduced total blood loss by 20% to 25%, and Seo et al. [21] reported reductions by 50% or more. In this study, the average total blood loss was reduced by 36% in Group 1 and 49% in Group 2 compared to Group 3, indicating that the amount of blood loss was lower after intra-articular TNA injection. The least amount of blood loss was in Group 2, which did not use a suction drainage tube, and was significantly lower than Groups 1 and 3 (P<0.0001). The average drainage amount reduced by approximately 48% with TNA (both groups) compared to without TNA (P<0.0001). Hidden blood loss increased in Group 2 (TNA only) compared to Group 1 (TNA with suction drainage tube), but it was most likely a result of not using the suction drainage tube. Wong et al. [20] reported no transfusion cases among 33 patients injected with 3.0 g of TNA intra-articularly in total knee arthroplasty. George et al. [22] reported that blood transfusions were performed in approximately 26% of cases without TNA and 2% of cases with TNA, and Seo et al. [11] reported that TNA injections in the articular cavity markedly reduced blood transfusion incidences. Therefore, TNA injections reduce blood transfusion frequency and volume. Song et al. [17] reported that 97% of cases with a suction drainage tube required transfusions but only 34% required transfusions without a suction drainage tube. They also reported that total blood loss decreased without a suction drainage tube. In this study, the blood transfusion frequency decreased in the groups using TNA. Notably, no transfusions were performed in Group 2, which used TNA and no suction drainage tube (P<0.0001), demonstrating that injecting TNA into the articular cavity without a suction drainage tube is the best method to reduce blood transfusions. Hemoglobin levels trended downwards in the TNA groups 1 to 3 days after surgery, particularly in Group 2 (P<0.0001). The hemoglobin reduction was the most remarkable on postoperative day 1, perhaps due to the short TNA half-life. The average postoperative platelet level did not significant differ among the groups, indicating that platelet activation was not affected (P=0.6618). The average postoperative fibrinogen level increased in the TNA groups, suggesting that TNA inhibited fibrinolysis (similar to results reported by Dahuja et al. [23]), but there was not statistically significant difference (P=0.3750). The average postoperative D-dimer was significantly lower in the TNA group, indirectly supporting the anti-fibrinolytic effect of TNA (P<0.0001). In particular, the results were lower in Group 2, suggesting that if the suction drainage tube is not used, then TNA remains in the articular cavity longer, sustaining the fibrinolysis inhibitory effect. The postoperative average PT and a PTT (Activated Partial Thromboplastin Time) were lower in the TNA groups. PT was dependent on the amount of tissue factor released from the damaged tissue, reflected by exogenous coagulation; TNA may have influenced this mechanism. Kazunari et al. [24] reported that using TNA in total knee arthroplasty reduced knee swelling. In this study, the swelling of the knee, thigh, and calf decreased in the TNA groups compared to without TNA. Thigh and calf swelling increased slightly in Group 2 (no suction drainage tube) compared to Group 1 (with suction drainage tube). However, the swelling diminished roughly six weeks after surgery without affecting the knee range of motion. TNA is a known cause of thromboembolic complications as it inhibits fibrin dissolution, which is a normal defense mechanism for preventing blood clots. However, Tan et al. [25] reported that using TNA in total knee arthroplasty does not affect venous thrombosis or other complications. Chen et al. [26] also reported in a meta-analysis that large amounts of TNA did not increase the DVT incidence rate. In this study, DVT occurred in two cases with TNA and in one case without TNA, but there were no serious complications (e.g., pulmonary embolism). This study was limited by the lack of a control group (i.e., no TNA injection and no suction drainage tube). Additionally, there were more female patients than male patients because female patients have low preoperative hemoglobin levels, which may affect blood transfusions. Nevertheless, considering blood transfusions and the potential complications are risky, reducing the transfusion frequency is crucial. Thus, injecting TNA into the articular cavity and omitting a suction drainage tube is a simple and effective method for reducing blood loss and the allogeneic blood transfusions frequency.

Conclusion

Intra-articular TNA injections during total knee arthroplasty considerably reduced the total blood loss, blood transfusion frequency, and leg swelling after surgery without complications. Therefore, if TNA is used in total knee arthroplasty, we recommend not using a suction drainage tube.

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