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Effect of Tranexamic Acid on Blood Loss and Blood Transfusion Reduction after Total Knee Arthroplasty

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Purpose: Total knee arthroplasty (TKA) accompanies the risk of bleeding and need for transfusion. There are several methods to reduce postoperative blood loss and blood transfusion. One such method is using tranexamic acid during TKA. The purpose of this study was to confirm whether tranexamic acid reduces postoperative blood loss and blood transfusion after TKA.
Materials and Methods: A total of 100 TKA patients were included in the study. The tranexamic acid group consisted of 50 patients who received an intravenous injection of tranexamic acid. The control included 50 patients who received a placebo injection. The amounts of drainage, postoperative hemoglobin, and transfusion were compared between the groups.
Results: The mean amount of drainage was lower in the tranexamic acid group (580.6±355.0 mL) than the control group (886.0±375.5 mL). There was a reduction in the transfusion rate in the tranexamic acid group (48%) compared with the control group (64%). The hemoglobin level was higher in the tranexamic acid group than in the control group at 24 hours postoperatively. The mean units of transfusion were smaller in the tranexamic acid group (0.76 units) than in the control group (1.28 units).
Conclusions: Our data suggest that intravenous injection of tranexamic acid decreases the total blood loss and transfusion after TKA.

Keywords: **Knee, Arthroplasty, Transexamic acid, Blood loss, Transfusion**

Introduction

Total knee arthroplasty (TKA) is one of the most successful orthopedic surgeries in relieving pain and restoring joint function in end-stage osteoarthritis, either degenerative or secondary to inflammatory arthritis, trauma, tumors, or infection around the knee joint[1-5]. However, the surgery is accompanied by an unavoidable risk of bleeding and subsequent requirement of blood transfusion[1-3]. Transfusion of blood products is not a benign procedure and is associated with many possible risks such as infection, acute systemic reactions, and death[4]. Transfusions also lengthen rehabilitation time and hospital stay and increase the cost for the patient[5,6]. Therefore, blood loss control during and after surgery is an important consideration to achieve good results after TKA. Methods to reduce postoperative blood loss and avoid allogeneic blood transfusions include autologous blood transfusion, hypotensive anesthesia[7], use of fibrin tissue adhesive[8], drain clamping[9-12], and administration of tranexamic acid[13-15]. Tranexamic acid administration during TKA surgery is one of most studied method. Studies have reported tranexamic acid reduced blood loss and the amount of blood needed in transfusions[13,16]. The administration of tranexamic acid also reportedly reduces the decrease in hemoglobin levels after TKA[17]. A meta-analysis of 12 studies concluded intravenous tranexamic acid injections reduced blood transfusion and blood loss in TKA and total hip arthroplasty (THA) without increasing the risk of thromboembolic complications[18]. Another meta-analysis of nine randomized controlled trials concluded the use of tranexamic

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acid for patients undergoing TKA reduced the requirement of blood transfusion[19]. In these studies, however, the blood loss was measured as the loss during surgery plus the drainage volume. Since there may also have been hidden losses as a result of hemolysis and tissue extravasation, which would not have shown on drain output, the true effect of tranexamic acid on blood loss was not clear[20]. A true estimate of total blood loss can be more appropriately made using a hemoglobin balance method[20,21]. The calculated blood loss based on hemoglobin drop and body volume takes into consideration both the hidden and evident losses. The purpose of this study was to assess the effect of tranexamic acid on total blood losses including hidden and evident losses through hemoglobin balance method[21]. We hypothesized that tranexamic acid would decrease the total blood loss during TKA measured using a hemoglobin balance method[21].

Materials and Methods

1. Inclusion and Exclusion Criteria

The study was approved by the Institutional Review Board of the Chonnam National University Bitgoeul Hospital. This prospective comparative study was conducted in a single institution based in two hospitals. All patients with primary end-stage knee osteoarthritis (Kellgren-Lawrence grades, 3–4) awaiting surgery were eligible for the study. We excluded patients with secondary osteoarthritis (e.g., rheumatoid arthritis, posttraumatic osteoarthritis, gouty arthritis), a cardiovascular problem (e.g., myocardial infarction, atrial fibrillation, angina, heart failure), simultaneous bilateral TKA, a history of thromboembolic disease, bleeding disorder, known allergy to tranexamic acid, and lifelong warfarin therapy for thromboembolism prophylaxis. A total of 100 patients were evaluated during the study period. Patients undergoing TKA were prospectively divided into one of the two study groups using sealed, opaque envelopes that were opened immediately before surgery.

2. Methods of Tranexamic Acid and Outcome Assessment

In the tranexamic acid group, patients received tranexamic acid intravenously (10 mg/kg) 10 minutes before tourniquet deflation and again at 3 hours postoperatively[22,23]. This regime was based on successful outcomes in literature and our own experience. In the control group, patients received a placebo 5 mL 0.9% normal saline at the similar timings of the tranexamic acid group. Preoperative data included age at the time of the operation, gender, and preoperative hemoglobin level. There were no differences between groups regarding the preoperative data (Table 1). Hemoglobin levels were measured 2 weeks preoperatively and 6 hours, 24 hours, 48 hours, and 5 days postoperatively. Total losses were calculated based on a 'hemoglobin balance method' described in literature[21]. This method estimates the blood volume of a patient based on the postoperative hemoglobin drop. The lowest value of the postoperative hemoglobin level obtained until the 5th postoperative day was used to calculate the hemoglobin drop. Transfusions were performed in compliance with our hospital policy. Blood transfusions were planned for asymptomatic patients with a hemoglobin level of <8.0 gm%. Transfusions were undertaken for patients with a level of <10.0 gm% only if they had 1) symptoms that were not well tolerated, were related to anemia, and could not be attributed to another cause (myocardial ischemia or hypoxemia) or 2) ongoing blood loss[24].

3. Surgical Technique

All operations were performed or supervised by two surgeons (EKS and JKS) using a midline skin incision and medial parapatellar arthrotomy. A posterior-stabilized type implant was used and the patella was not resurfaced in all cases. All patients received general or spinal anesthesia depending on the discretion of the anesthesiologist. A dose of 1 g cetrazole was given intravenously shortly before the operation. A tourniquet was applied around the upper thigh after elevation of the limb and exsanguination with an Esmarch bandage and inflated to a pressure of 280 mmHg before skin incision. An intramedullary alignment rod was used for femoral cutting and an extramedullary guide system was used for tibial cutting. Meticulous electric cauterization of the soft tissue bleeding points was performed throughout the surgery. The tourniquet was not released until skin closure and application of a compressive dressing. Intraoperative blood loss was negligible in all patients because the tourniquet was not deflated until wound closure. In each knee, one intra-articular drain was applied and connected to a high-vacuum drain bottle. The patients were asked to utilize an intermittent sequential

Table 1. Demographic Details of Patients in Both Groups

Variable	Control group (n=50)	Tranexamic acid group (n=50)	p-value
Age (yr), mean (range)	68.3 (52–83)	70.2 (55–86)	0.054
Sex (M:F)	2:48	7:43	0.089
Hemoglobin (gm%), mean±SD	12.5±1.4	12.3±1.6	0.441
Body mass index (kg/m^2)	24.8	24.4	0.861

SD: standard deviation.

pneumatic compression device for deep vein thrombosis (DVT) prophylaxis as soon as possible. The compressive dressing and Foley catheter were removed on the first day after surgery. The drains were emptied every day and the amount of drained blood was measured. The drains were removed only when this amount was less than 100 mL for 24 hours. On average, drains were kept for 3 days (range, 2 to 5 days). This has been our institution's policy, as we have observed that removal of drains at one preselected time may not work in all cases. Some cases have collection for longer periods and early removal in such cases may not only cause erroneous lower recordings of drained blood but also has a risk of hematoma formation. Both groups followed a standard postoperative rehabilitation protocol, including continuous passive motion of the knee and muscle strengthening exercises on the first day after surgery. All patients were asked to get out of bed with walker support on the afternoon of the first postoperative day to decrease the incidence of DVT, as described by Pearse et al.[25]. Mechanical DVT prophylaxis using a pneumatic compression device was performed in all patients. Considering the low incidence of DVT in Asian populations[26], routine use of pharmacological prophylaxis was not prescribed according to our institutional policy. Routine screening for DVT was not done for asymptomatic patients. Symptomatic patients with excessive calf swelling and pain were screened for DVT using Doppler ultrasonography and computed tomography angiography. All patients at discharge were explained about warning symptoms of infection and DVT and were asked to report immediately to the emergency department in case of development of such symptoms.

4. Data Evaluation

The total volume of drained blood and the decrease in hemoglobin at 6 hours, 24 hours, 48 hours and 5 days postoperatively were recorded. Blood transfusions were recorded as the number of units of packed erythrocytes. All patients were discharged from the hospital after two weeks of surgery. All quantitative data were expressed as mean±standard deviation. Statistical significance of differences in the mean values of continuous variables such as age, preoperative hemoglobin, total volume of drained blood, and postoperative decrease in hemoglobin level were determined using Student *t*-test. Chi-square test was used for categorical data including the need for blood transfusion. SPSS ver. 14.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. A p-value less than 0.05 was considered to indicate statistical significance. All aspects of the statistical analysis were reviewed by a statistician.

Results

The mean postoperative total volume of drained blood was lower in the tranexamic acid group (580.6±355.0 mL) than in the control group (886.0±375.5 mL) (p=0.002). There was a reduction in the transfusion rate in the tranexamic acid group compared with the control group (40% vs. 64%; p=0.016). The mean units of transfusion were smaller (p=0.007) in the tranexamic acid group than in the control group (0.76 units vs. 1.28 units). The hemoglobin level at 6 hours postoperatively was similar (p=0.801) in the two groups, but it was greater in the tranexamic acid group than in the control group at 24 hours, 48 hours, and 5 days postoperatively at statistically significant levels (Table 2). The hemoglobin drop was calculated as the difference between the lowest postoperative hemoglobin level and the preoperative hemoglobin level. This drop was significantly high for the control group (2.8 gm/L) compared to the tranexamic acid group (1.7 gm/dL) (p=0.000). The total amount of blood loss calculated using the hemoglobin balance method[21] was significantly less in the tranexamic acid group than in the control group (p=0.002) (Table 2). There were no cases of symptomatic DVT or pulmonary embolism (PE) in both groups during the 3 months of follow-up. Table 3 shows the amount of evident blood loss on each postoperative day measured based on the drain output and the number

Table 2. Postoperative Hemoglobin, Total Drain Output, and Blood Transfusion

Variable	Control group (n=50)	Tranexamic acid group (n=50)	p-value[a]
Total volume of drained blood (mL)	886±375.5	580.6±355.0	0.002
No. of patients receiving transfusion (%)	32 (64)	20 (40)	0.016
Mean units of transfusion (unit)	1.28	0.76	0.007
Hemoglobin (g/dL) postoperative			
6 hr	11.0±2.1	11.1±2.3	0.801
24 hr	10.2±1.7	10.9±1.3	0.042
48 hr	9.5±1.4	10.5±1.6	0.002
5 day	10.1±2.1	10.8±2.2	0.048
Hemoglobin drop	2.8±0.8	1.7±0.5	0.000
Total loss (mL)	1,404	913	0.002

Values are presented as mean±standard deviation.
[a]p-values are for unpaired two-tailed Student *t*-test, except for blood transfusion which is for chi-square test.

Table 3. Postoperative Drain Output

Variable	Control group (n=50)	Tranexamic acid group (n=50)	p-value[a)]
POD 1	611.6±227.1 (50)	367.1±249.0 (50)	0.009
POD 2	151.0±96.9 (41)	146.6±68.3 (43)	0.798
POD 3	133.1±58.0 (27)	125.0±54.2 (21)	0.634
POD 4	121.8±41.2 (15)	98.2±28.6 (8)	0.054

Values are presented as mean±standard deviation (number).
POD: postoperative day.
[a)]p-values are for unpaired two-tailed Student *t*-test.

of patients still utilizing the drain. Postoperative day 1 losses were significantly different between the groups, but no difference was found on subsequent days.

Discussion

The most important finding of the current study is that intravenous tranexamic acid decreased the perioperative blood loss, calculated total blood loss, hemoglobin drop, and need for transfusion. Furthermore, this method did not cause an increase in the incidence of thromboembolic events.

Surgical trauma after arthroplasty results in a hyperfibrinolytic state[27)]. Since early postoperative bleeding is the result of a shift in the hemostatic mechanism towards fibrinolysis, the anti-fibrinolytic drugs such as tranexamic acid are very effective to control bleeding. We agree with most reports in literature describing the reduction in blood loss as ranging 30%–50%[13-15)]. Most of these reports have evaluated blood losses in drains at 24–48 hours after surgery. Similar to these results, we also observed a reduction of 40% in blood loss on postoperative day 1 (367 mL vs. 611 mL).

The difference in drain output between two groups was observed particularly on 1st postoperative day. This was primarily because tranexamic acid has a half-life of 3 hours and it remains in the extravascular tissue up to 17 hours[28)], after which it has no effect on postoperative bleeding. Therefore, postoperative bleeding after 1st postoperative day showed no significant difference between two groups. Despite this, the overall blood loss in the tranexamic acid group was 35% less than that in the control group. This was because most bleeding after arthroplasty tends to occur during the first 24 hours[1-5)].

We found that tranexamic acid was effective in decreasing not only the evident blood loss but also the total blood loss based on the calculation using the hemoglobin balance method. It is difficult to compare total losses in most studies, as there is no uniform criterion for measurement. Most studies have not calculated total losses[22,23)]. Few studies have used hematocrit drop[29,30)] while others have used hemoglobin drop[24)]. Some studies have taken 2nd postoperative day hemoglobin values[31)] while others have used 4th postoperative day values[21)] for calculation. We believe that hemoglobin usually decreases for initial 3–5 days after surgery and then begins to rise. The lowest value measured during this period best shows the true loss. Therefore, instead of a fixed day value, we used the lowest hemoglobin value for our calculation. We saw a reduction of 37% in total blood loss in the tranexamic acid group compared to the control group. Despite the utilization of different methods for calculation, most authors have shown tranexamic acid decreases total blood loss[21,29,30)].

We also observed a 24% decrease in the need for transfusion in the tranexamic acid group, and this reduction was statistically significant in consensus with data in literature. In addition, not only was the number of patients requiring transfusions less, the total number of transfusions required for each patient was significantly less in the tranexamic acid group compared to the control group. The rate of transfusions in our study was a little high in both groups probably because of the female predominance; females tend to have lower preoperative hemoglobin levels compared to those of males. In our study, the postoperative hemoglobin was between 8–10 gm% at the time of transfusion in most of the patients who were transfused (16 in tranexamic acid group and 24 in control group) due to tachycardia not responding to fluid management; however, transfusion trigger has mostly been less than 8 gm% in literature[21,24)].

Tranexamic acid creates a prothrombotic state by inhibiting fibrinolysis. This raises the concern of DVT. However, we observed no adverse effects of tranexamic acid in terms of the development of symptomatic DVT and PE. The safety of tranexamic acid has been well established in literature. Recent reviews and meta-analyses have found no increased risk of thromboembolic events. They found that perioperative intravenous tranexamic acid administration was not associated with increased risk of complications.

We recognize limitations to our study. First, the sample size (100 patients) was too small to address some questions. Second, the study design was not double-blinded, randomized and can only be regarded as a prospective comparative trial. Third, the operations were performed by only two (EKS and JKS) of the total authors of this study. Fourth, the female to male ratio in our study was high because most TKA patients in our country are females. Female patients may have lower preoperative hemoglobin levels and greater blood transfusion rates after TKA than males; however, the ratios of females to males and the preoperative he-

moglobin levels were not different between the two groups in the study. Lastly, intraoperative anesthetic technique was determined based solely on the discretion of an anesthesiologist. This may have affected the total blood loss, and a study using a different anesthetic technique may be more appropriate. However, there was no statistically significant difference in the ratio of spinal to general anesthesia between the groups both groups, and thus we believe any effect the anesthetic technique could have on the results would have been the same in both groups.

Conclusions

In conclusion, our prospective comparative study showed that the preoperative and postoperative single injection of tranexamic acid could be effective in reducing total blood loss and the need for blood transfusion after TKA for patients without any history of thromboembolic disease.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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