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The comparative efficacies of intra-articular and IV tranexamic acid for reducing blood loss during total knee arthroplasty

Jai-Gon Seo · Young-Wan Moon · Sang-Hoon Park · Sang-Min Kim · Kyung-Rae Ko

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Abstract

Purpose Reduction in blood loss during surgery stabilizes hemodynamic status and aids in recovery after total knee arthroplasty (TKA). In this study, the authors examined whether different administration routes of tranexamic acid (TNA) might affect the amount of blood loss after TKA.

Methods A total of 150 patients were prospectively allocated to each of the three groups (intravenous, intra-articular, and placebo group) and underwent unilateral TKA. During closing the operative wound, TNA (1.5 g mixed in 100 cc of saline) was administered intravenously or intra-articularly according to the enrolled group, and an equivalent volume of normal saline was administered into the knee joint cavity and intravenously in the placebo group, respectively. The amount of blood loss and transfusion, and changes in haemoglobin levels were documented accordingly.

Results The mean blood loss in the intravenous, intra-articular, and placebo groups were 528 ± 227, 426 ± 197, and 833 ± 412 ml, respectively. About 66 % (intravenous), 80 % (intra-articular), and 6 % (placebo) of each group did not require transfusion for any reason, and the mean amount of transfusion was 273.6, 129.6, and 920.8 ml, respectively. Preoperative haemoglobin values decreased by 1.6 ± 0.8, 1.8 ± 0.8, and 2.0 ± 0.9 mg/dl, respectively.

Conclusion Compared to intravenous administration, intra-articular administration of TNA seems to be more effective in terms of reducing blood loss and transfusion frequency. TNA may improve the general conditions of patients given TKA by maintaining a hemodynamically stable state, aiding in recovery, and reducing the chance of transfusion-associated side effects and complications.

Level of evidence II.

Keywords Blood loss · Tranexamic acid · IV injection · Intra-articular injection · Total knee arthroplasty

Introduction

Previous studies reported that as much as 1,000–1,790 ml of blood was lost during total knee arthroplasty (TKA) [5, 6, 20] and that 10–38 % of patients required 1–2 units of allogenic blood transfusion accordingly [3, 12, 14, 19]. Since the side effects and complications are rather common after transfusion, maintaining hemodynamic stability seems to be important and aids in fast recovery after TKA [7].

In order to reduce blood loss during TKA, many methods have been introduced, such as, autologous transfusion [26], hypotensive anaesthesia [17], drain clamping [25, 26], the application of fibrin tissue adhesive [21] or a compression bandage, and cryotherapy [10, 16]. Additionally, intravenous (IV) or intra-articular administration of tranexamic acid (TNA) is known to reduce transfusion frequency and bleeding before and after surgery [11, 13, 14, 16, 19, 23, 30, 31, 33].

J.-G. Seo · Y.-W. Moon · S.-M. Kim · K.-R. Ko
Department of Orthopaedic Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

S.-H. Park (✉)
Department of Orthopaedic Surgery, National Health Insurance Corporation Ilsan Hospital, Ilsan-ro 100, Ilsandong-gu, Goyang, Kyunggi-do 410-719, South Korea
e-mail: orthomania@gmail.com

Tranexamic acid is an antifibrinolytic agent that activates plasminogen and stops bleeding by inducing blood clot formation [4, 14, 20, 29, 30]. At present, TNA is used to stop excessive bleeding during dental [29], cardiac [1, 9], spine [32], and hip surgeries [5, 20]. However, little information is available regarding the comparative efficacy of TNA according to the administration route. Thus, this study was prospectively designed to determine which administration route of TNA is more efficacious hemodynamically after TKA. It was hypothesized that intra-articular administration of TNA would significantly reduce the blood loss and help maintaining hemodynamical stability.

Materials and methods

This prospective, randomized, placebo-controlled study was performed on 150 patients who underwent unilateral TKA from 1 May 2011 to 31 September 2011. Before starting this trial, the study protocol was approved by our institutional review board.

The inclusion criterion was patients aged between 55 and 80 years who planned to undergo TKA due to degenerative arthritis on a knee joint. Exclusion criteria were as follows: patients with any cardiovascular problems (such as myocardiac infarction history, atrial fibrillation, angina), patients with cerebrovascular conditions (such as previous stroke or vascular surgery history), patients with thromboembolic disorders, or those exhibiting a deteriorating general condition.

Patients were randomly allocated to each of the intravenous, intra-articular, and placebo groups using a random number list. There were no differences in the demographic factors among groups (Table 1).

Operation procedures and postoperative protocol

All patients underwent TKA using extramedullary alignment technique by a single surgeon (JGS). After applying a pneumatic tourniquet, approaches were made using a modified antero-medial parapatellar incision. After soft tissue balancing, extramedullary minimal invasive surgery (EM-MIS) technique was used to resect femoral and tibial bones [28], and same types of prosthesis (Scorpio® NRG, Stryker, NJ) were fitted for all patients. Meticulous electric cauterization of soft tissue bleeding was performed during surgery.

For patients in the intravenous group, 1.5 g of TNA in 100 cc of saline was administered immediately after closing surgical sites. In intra-articular group, patients were given 1.5 g of TNA in 100 cc of saline directly into the knee joint cavity while suturing. Patients in placebo group were administered an equivalent volume of normal saline into the joint space and intravenously.

Tourniquets were not released until finishing skin closure. Two intra-articular drains were left in situ for 24 h for postoperative bleeding. After removal of drains, ROM exercise and walker-aided ambulation were encouraged. All the patients were followed up postoperatively after 2 months.

Outcome measures

The amount of drainage was recorded in order to estimate the blood loss during TKA, and the difference in haemoglobin levels between the preoperative and the postoperative lowest one was also calculated. The frequency of transfusion, the number of blood units transfused, any perioperative complications or events such as infection, deep vein thrombosis (DVT), and pulmonary embolism were also recorded accordingly.

The necessity for transfusion was determined based on the guidelines for perioperative transfusion by the National Institutes of Health Consensus Conference, which suggested that decision should be made based on the clinical assessment aided by laboratory data, patients' symptoms and anaemic signs. Thus, transfusion was allowed only for the patients whose haemoglobin level was less than 8.0 g/dl

Table 1 Demographic factors

Parameters	Intra-articular injection group ($n = 50$)	IV injection group ($n = 50$)	Placebo group ($n = 50$)	p value
Age (years)	67.5 ± 6.6	66.8 ± 6.3	67.8 ± 6.1	NS
Gender: male/female	5/45	6/44	5/45	NS
Height (cm)	154.3 ± 7.3	155.1 ± 7.2	154.1 ± 6.1	NS
Body mass index (kg/cm^2)	27.8 ± 3.5	28.1 ± 3.1	27.9 ± 3.3	NS
Preoperative flexion contracture (°)	7.5 ± 6.3	8.6 ± 5.3	7.6 ± 6.1	NS
Preoperative further flexion (°)	128.7 ± 14.7	129.1 ± 14.1	129.1 ± 14.1	NS
Skin incision (cm)	9.3 ± 1.2	9.1 ± 1.0	9.3 ± 1.1	NS
Operation time (min)	54.6 ± 14.3	54.1 ± 1.4	55.1 ± 1.4	NS

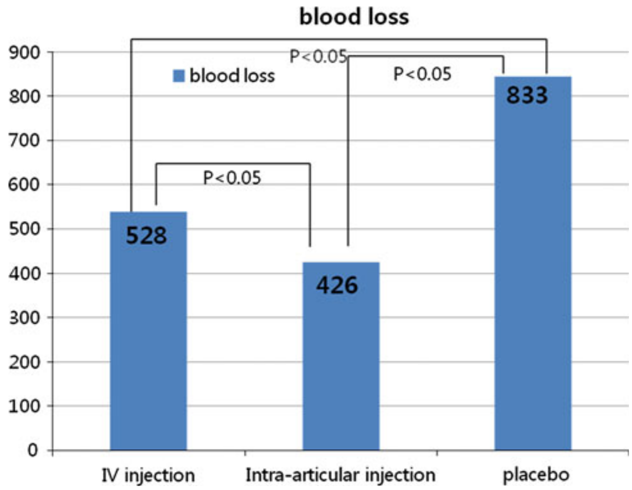

Fig. 1 The postoperative blood loss. Mean blood losses during surgery in the IV, intra-articular, and placebo groups were 528 ± 227, 426 ± 197, and 833 ± 412 ml, respectively, which were significant intergroup differences

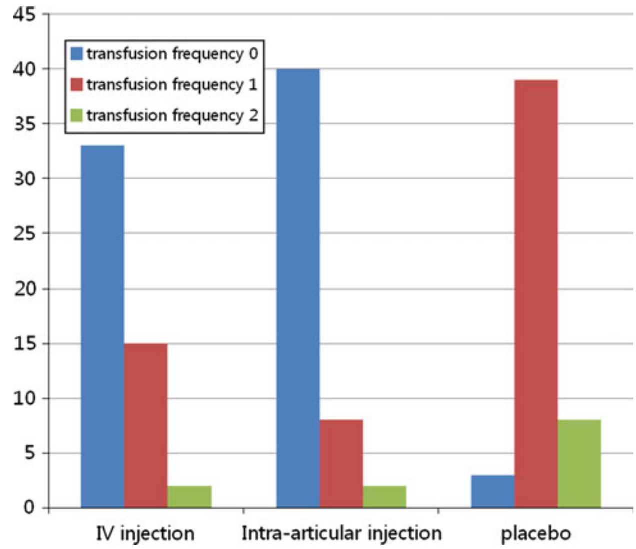

Fig. 2 The frequency of transfusion among the IV, intra-articular TXA injection group, and placebo group; 33 (66 %), 40 (80 %), and 3 (6 %) patients did not require a transfusion, and these differences were significant

or whose haemoglobin level was less than 10.0 g/dl with concomitant intolerable anaemic symptoms or any anaemia-related organ dysfunctions.

Statistical analysis

The Kruskal–Wallis test was used to analyse the amount of blood loss, difference in haemoglobin levels, the amount and frequency of transfusion. Post hoc analysis was conducted with the multiple comparison Tukey's test using ranks to test the null hypothesis. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA), and statistical significance was accepted for p values of <0.05.

Results

Mean blood losses during surgery in the intravenous, intra-articular, and placebo groups were 528 ± 227, 426 ± 197, and 833 ± 412 ml, respectively, with significant intergroup differences (p value <0.001) (Fig. 1). Both TNA groups resulted in significantly less amount of blood loss compared to the placebo group, and among the TNA groups, intra-articular administration of TNA yielded less blood loss than intravenous injection.

Among 50 patients in each group, 33 (66 %) in intravenous, 40 (80 %) in intra-articular, and 3 (6 %) in placebo did not require transfusion (p value <0.001) (Fig. 2).

The average amounts of transfusion (packed RBCs) were also significantly different among groups and were 273.6 ml in intravenous, 129.6 ml in intra-articular, and 920.8 ml in placebo, respectively (p value <0.001) (Table 2).

Compared to preoperative haemoglobin level, postoperative one decreased by 1.6 ± 0.8, 1.8 ± 0.8, and by 2.0 ± 0.9 mg/dl in the intravenous, intra-articular, and placebo groups, respectively (Table 2).

Postoperative complications included 5 cases of DVT and 2 cases of atrial fibrillation. Two cases of DVT developed in the placebo group and 3 in the intravenous group, and one case of atrial fibrillation was encountered in each of the placebo and intravenous group. The frequency of complications in each group was not statistically significant. No fatal complication, such as pulmonary embolism, occurred among study groups. Patients with DVT or atrial fibrillation were discharged from hospital after symptomatic improvement (Table 3).

The average range of motion (ROM) at 2 months were 2.6°–123.3°, 2.5°–120.4°, and 2.9°–124.1° in the intravenous, intra-articular, and placebo groups with no significant statistical difference in intergroup analysis.

Discussion

The most important finding of the present study is that TNA reduces blood loss in TKA and the need for transfusion accordingly. Comparing two TNA groups, intra-articular injection of TNA seems to be more effective than intravenous injection in terms of the amount of blood loss and the need for transfusion.

Intra-articular injection at the surgical site provides direct and straightforward means of application before

Table 2 Blood loss, transfusion amounts, preoperative haemoglobin–postoperative haemoglobin differences

Parameters	Intra-articular injection group ($n = 50$)	Intravenous injection group ($n = 50$)	Placebo group ($n = 50$)	p value
Blood loss	426 ± 197 ml	528 ± 227 ml	833 ± 412 ml	<0.001
Transfusion amounts	129.6 ± 280 ml	273.6 ± 468 ml	920.8 ± 324 ml	<0.001
Preoperative Hb	11.5 ± 1.3 mg/dl	11.3 ± 1.7 mg/dl	11.6 ± 1.2 mg/dl	NS
Preoperative Hb–postoperative Hb (decreased Hb)	−1.8 ± 0.8 mg/dl	−1.6 ± 0.8 mg/dl	−2.0 ± 0.9 mg/dl	<0.001

Table 3 Postoperative complications

	Intra-articular injection group ($n = 50$)	IV injection group ($n = 50$)	Placebo group ($n = 50$)	p value
Number of DVT	3	0	2	NS
Number of atrial fibrillation	1	0	1	NS
Number of pulmonary embolism	0	0	0	NS

DVT deep vein thrombosis

tourniquet releasing [16, 33]. In addition, intra-articular TNA injection has the advantage of inducing partial microvascular haemostasis by stopping fibrin clot dissolution in the affected area. Once injected intra-articularly, TNA is rapidly absorbed and maintains a biological half-time of approximately 3 h within joint fluid [13, 19, 20, 23].

A concern exists on the use of TNA that antifibrinolytic effect of TNA may cause thromboembolic complications in patients given TKA [2, 18, 25, 30]. Due to the concern, patients with a history of a cardiac problem or with a thromboembolic disease were excluded from this study enrolment, and a relatively low dose of TNA was administered based on the review of previous studies. We suspect that the complication rate following TNA administration is small because systemic absorption is low when administered intra-articularly. Furthermore, no thromboembolic complications such as DVT or pulmonary embolism have been encountered after intra-articular injection of TNA in the present or in the previous studies [1, 15, 33]. However, our results lacked statistical significance, and thus, a larger-scale study is required. According to the meta-analyses conducted on the topic, the risk of venous thromboembolism is not increased by TNA, but great care is mandatory in patient selection and in the choice of administration route and dosage because of the antifibrinolytic effect of TNA [4, 12, 18].

Previous relevant studies have been conducted in various protocols including different TNA dosages to reduce blood loss and transfusion frequency [2, 13, 30, 32, 33]. The results revealed that high TNA dosages did not increase the frequency of thromboembolic complications. Despite the promising results of use of high TNA doses, the lowest effective dosage seems to be desirable to minimize the potential thromboembolic complications after TNA administration. Others have argued that TNA is effective for reducing blood loss but does not reduce transfusion amounts or frequencies since, although TNA decreases over 50 % of drainage and reduces blood loss. TNA still cannot reduce hidden blood loss [12, 27].

In the present study, intra-articular and intravenous use of TNA resulted in less blood loss through drainage and reduced transfusion frequencies and amounts. Thus, TNA seems to improve the general conditions of patients given TKA by maintaining a hemodynamically stable state and by reducing the transfusion-associated side effects and complications. In particular, TNA use may aid early rehabilitation and functional recovery, and reduce hospital stay by reducing the risk of an anaemic status [8, 24].

The overall blood loss in this study was also less compared to the blood loss in general conventional TKA. As explained in the "Materials and methods" section, all TKAs were performed using less invasive EM-MIS technique, which, we believe, caused overall less blood loss. Since the severity of medullary canal injury is reduced by the EM method and soft tissue injury is reduced by MIS, perhaps over 1,000 ml of blood loss could be prevented [16]. According to Lin et al. [22], blood loss of up to 1,453 ml (733–2,537 ml) occurs during MIS-TKA, and about 20 % of blood loss was prevented when intravenous TNA administration was applied to MIS-TKA group. Wong et al. [33] also reported that intra-articular TNA use achieved more than 400 ml reduction in blood loss compared to 1,610 ml (1,480–1,738) loss observed in the placebo group, with 1,208 ml (1,078–1,339 ml) in the 3.0 g TNA group and 1,295 ml (1,167–1,422 ml) in 1.5 g TNA group. Compared to Wong's study, our results demonstrated reduction in blood loss by at least 400 ml in all groups, and the blood loss in placebo group was even less than conventional TKA group with TNA use.

Several limitations should be considered in this study. First, although the present study was conducted with a relatively larger number of patients than previous studies, its statistical power was not high enough, and thus, further studies are required to confirm our findings. Second, because all surgeries were performed using the EM-MIS technique, we were unable to compare our findings with conventional TKA under the same circumstance. Third, ultrasonographic study on asymptomatic DVT occurrence and study on blood concentration of TNA after surgery were not progressed. Forth, the effects of TNA on rehabilitation and recovery were not investigated. Despite the potential limitations, the advantage of this study is that it is the most extensive study to date conducted in prospective randomized controlled design [12, 16, 20, 30].

The intra-articular use of TNA in TKA patients showed less blood loss through drainage and reduced transfusion frequencies and amounts. Furthermore, intra-articular TNA injection is easy to perform and cost-effective as compared with topical sealants. Thus, TNA may play a part in improving the general conditions of patients given TKA by maintaining a hemodynamically stable state and reducing the chance of transfusion-associated side effects and complications.

Conclusion

This prospective comparative study showed that during TKA, TNA reduced blood loss and helped reducing transfusion amounts and frequencies with negligible side effects. With regard to administration route, intra-articular administration of TNA seemed to be more effective than intravenous injection in terms of blood loss and transfusion frequency.

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