RESEARCH ARTICLE

A comparison of the effects on postoperative bleeding of the intra-articular application of tranexamic acid and adrenalin in total knee arthroplasty

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Abstract

Objective: To compare the efficacies of intra-articular applications of tranexamic acid and adrenaline on postoperative bleeding after total knee arthroplasty.

Methods: The single-center, retrospective, controlled study was conducted at Selcuk University , department of orthopedics surgery and comprised data of patients who underwent primary, unilateral, cemented total knee arthroplasty between July 2012 and December 2014. Group 1 had received tranexamic acid 1g after closure of articular capsule. Group 2 had received adrenalin. Group 3, the control group, received no medication intra-articularly after total knee arthroplasty. The amount of blood collected in the drain and postoperative alterations in haemoglobin and haematocrit values were compared.

Results: Of the total 90 subjects, there were 30(33.33%) in each of the three groups. The decrease of haemoglobin and haematocrit values in Group 1 was statistically significant compared to both Group 2 and Group 3 ($p<0.05$). The amount of blood collected in the drains was remarkably lower in Groups I and 2 compared to Group III ($p<0.05$). No deep venous thrombosis or pulmonary emboli were encountered across the sample.

Conclusion: Intra-articular administration of tranexamic acid was found to be beneficial and safe for the achievement of effective haemostasis after total knee arthroplasty.

Keywords: Tranexamic acid, Adrenaline, Haemostasis, Blood loss, Total knee arthroplasty. (JPMA 69: 325; 2019)

Introduction

Currently, total knee arthroplasty (TKA) is considered the treatment of choice in advanced stages of knee osteoarthritis. Despite advances in surgical and anaesthetic techniques, TKA is still associated with considerable amount of perioperative blood loss. Postoperatively, blood continues to ooze from the cut-ends of bone, open intra-medullary canal and dissected soft tissues. Increased fibrinolytic activity, which is stimulated by surgical trauma, may also increase blood loss after TKA, at least during the early postoperative hours.

Anaemia due to surgical blood loss is not infrequent in patients undergoing TKA and is associated with high rate of allogenic blood transfusion in approximately 40% of cases.[1] In addition to the potential complications of blood transfusion, including transmission of infectious disease and transfusion-related reactions, it has been shown that blood transfusion compromises the outcome of TKA patients, prolongs hospital stay, and increases the risk of surgical site infection.[1,2] Although various measures and strategies, such as autologous blood transfusion and use of cell salvage systems, have been introduced, the safest and the most efficient perioperative blood conservation method has yet to be found.[3-5] Additionally, these strategies have limitations and are not cost-effective.[6,7] Using algorithmic approaches and determining predictors of perioperative bleeding and transfusion appear to be the main strategies which can lead to reduction in allogeneic blood use after joint arthroplasty.[8,9] Tranexamic acid (TXA) is an anti-fibrinolytic agent, which can effectively decrease postoperative bleeding by inhibiting the fibrinolytic activity. Intravenous (IV) or intra-articular (IA) administration of TXA have been proposed to reduce perioperative blood loss in TKA.[10-12] Recent literature has demonstrated the effectiveness of TXA on blood loss and transfusion rates without increasing rate of thromboembolism after TKA.[13,14] Similarly, IA adrenaline infusion during surgical closure is another method which has been recommended for the reduction of surgical bleeding and postoperative blood loss following TKA. Nevertheless, adrenaline can be associated with delayed wound healing, skin necrosis, haematoma, elevated blood pressure (BP) and deep venous thrombosis (DVT).[15,16] However, little information is available regarding the comparative efficacies of these two agents on postoperative bleeding following TKA. Thus, the current study was planned to determine if the use of TXA reduces perioperative blood loss and need for allogenic blood transfusion in patients undergoing TKA, to compare the effectiveness of intra-articularly administered TXA and adrenaline on perioperative blood loss, and evaluate the rate of complications, including the rate of thromboembolic

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events, in patients receiving TXA and adrenaline.

Material and Method

The single-center, retrospective, controlled study was conducted at Selcuk University, department of orthopedics surgery and comprised data of patients who underwent primary, unilateral, cemented total knee arthroplasty between July 2012 and December 2014. After approval was obtained from the institutional review board, the sample size was determined which was equal to the anticipated population according to result of our statistical power analyses. The power analysis are performed for testing the mean difference in haemoglobin and haematocrit and draninage and it is detected that the observed power as 0,971, 0,863 and 1 respectively. In this case our anova results are turstworthy with high power. Three groups were formed. Group 1 had received TXA 1g after closure of articular capsule. Group 2 had received adrenalin. Group 3, the control group, had received no medication intra-articularly after TKA. Exclusion criteria consisted of American Society of Anaesthesiologists grade IV (ASA-IV) or higher physical status, severe ischaemia and/or cardiac valvular disease, revision cases, collagen vascular disease, bilateral knee joint arthroplasty, hypersensitivity to TXA or adrenaline, coagulopathy, history of the thromboembolic disease and renal dysfunction (serum creatinine level >1.5 g/dl).

TXA and adrenalin were applied as retrograde via haemovac drain when the wound entirely closed. Haemovac drain was kept closed for 30 minutes after application. Group I received IA 4 ampul TXA (1 amp %5lik 5ml 250 mg TXA), while 1 ampul adrenaline (0,5mg/ml) diluted with 20ml of physiological saline was applied to Group 2.

A standard surgical procedure was carried out by the same surgical team and same cemented prostheses design (Vanguard-posterior stabilised type, Biomet USA) was utilized for all patients. First dose antibiotic prophylaxis (IV cefazolin 1 or 2g according to body weight) was administered one hour before the surgical procedure, and continued for 24 hours postoperatively. All surgical procedures were performed under spinal anaesthesia with the use of a thigh tourniquet and knee joint was accessed through a medial parapatellar arhtrotomy. Pharmacological DVT prophylaxis with low molecular weight heparin, (40-60 mg/daily, s.c) was given 12 hours before the procedure and continued for six weeks starting from 6th hour postoperatively. Anti-embolic stockings were administered and cryotheraphy was started in early postoperative period. Lower limb muscle contraction exercises were initiated as soon as possible after the spinal anaesthesia dissolved and muscular function recovered. Patients were mobilised day after the surgery and, and ambulation with assistive devices was encouraged for two or three weeks postoperatively. The same rehabilitation regimen was applied to all patients.

Haemoglobin (Hb) and haematocrit (Hct) levels were assessed preoperatively, and on 6th and 24th hours postoperatively. After surgery, drains were maintained for 24 hours. Blood volume collected in drains was recorded in all groups. Red blood cell (RBC) transfusion was not made if Hb level was $\geq$10 g/dl. In case of Hb level was between 8-10 g/dl, patients were assessed regarding clinical findings such as tachycardia, palpitation, dizziness and fatigue, and autologous blood transfusion was initiated accordingly. Routine RBC transfusion was, however, reserved for cases with Hb<8 g/dl. The amount of RBC suspension transfusion was noted for every patient.

Clinical examination data, including haemodynamic alterations and complications, were noted. Two staff members blinded to patients evaluated the data. The incidence of symptomatic DVT and pulmonary embolism was assessed until the 90th day. Pain, swelling of the limb, calf tenderness, superficial venous engorgement, and Homan's sign were assessed daily until the patient was discharged. In case of any pain or swelling at the calf or thigh, an initial evaluation for DVT was made with vascular doppler ultrasonography. Dyspnoea and chest pain, which may indicate pulmonary embolism, were also evaluated. Patients were followed up on the 30th and 90th days postoperatively and instructed to report any signs of DVT.

Baseline descriptive data, volume collected in the drain, pre- and postoperative Hb and Hct levels, changes in Hb and Hct levels on 24th hour, and the amount of RBC suspension transfused were noted and compared among the groups.

Comparison of groups was made using a parametric test, analysis of variance (ANOVA). Normality and homogenity of variance were tested with Kolmogorov-Smirnov and Levene tests to check the assumption of ANOVA, respectively. Tukey honestly significant difference (HSD) test was used for multiple comparisons. For all tests, the possibility for type 1 error was assumed as α=0.05.

Differences in groups regarding discrete data were evaluated with Cochran's test.

Quantitative variables were expressed as mean, standard deviation (SD), median, interquartile range (IQR), and min-max range. The confidence interval was 95%, and level of significance was set at p<0.05.

Result

Table-1: Comparison of baseline descriptive parameters in 3 groups. Comorbidities included systemic diseases such as diabetes mellitus, hypertension, cardiac disease and chronic obstructive pulmonary disease.

Variable	Groups			p Value
	I	II	III	
Gender (male/female)	5/25	7/23	7/23	0.75
Age (years)	65.66±6.91	65.83±4.94	68.30±6.51	0.19
Body mass index (kg/m^2)	32.86±3.77	33.73±3.37	31.84±3.53	0.13
Comorbidity (Yes/No)	13/17	14/16	16/14	0.73

(Group I: TXA; Group II: adrenaline; Group III: control).

Cochrane test is used to compare the three groups for ratio for male patients and ratio of comorbidity existence. Analysis of variance (ANOVA) is also used to compare the group's means in terms of age and body mass index (BMI).

Of the total 90 subjects, there were 30(33.33%) in each of the three groups. Mean age in Group 1, was 65.66±6.91 years, Group 2, 65.83±4.94 years, and Group 3, 68.30±6.51 years. Overall, 52(58%) patients were operated on the right side, while 38(42%) cases underwent TKA for the left knee. Among the groups, there was no significant difference in demographic characteristics (p>0.05) (Table-1)

No remarkable difference was observed in groups regarding Hb and Hct levels preoperatively or on 6th and 24th hours postoperatively. But when all the groups were compared in terms of preoperative Hb and Hct with postoperative values, the decrease was significantly lower in Group 1 compared to Group 2 and Group 3 (p<0.05). The decrease of Hb and Hct values were lower in Group 2 compared to Group 3 but it was not statistically significant (p>0.05) (Table-4, 5). When the groups were compared for amount of blood in drains, the amount was significantly lower in Group 1 and 2 compared to Group 3 (p<0.05), and also the amount of blood was significantly lower in Group 1 compared to Group 2 (p<0.05). The volumes collected in the drain were significantly different for all groups (Table-2). Group 1 had the lowest volume collected in the drain, while Group 3 had the highest volume (Table-3).

Table-3: Statistical evaluation of the amount of blood coming from the drain.

		N	Subset for alpha = .05		
		1	1	2	3
Group	Transamin	30	321,6667		
	Adrenalin	30		615,0000	
	Control	30			800,0000
	Sig.		1,000	1,000	1,000

DRAIN
Tukey HSD.

Table-4: Statistical evaluation of haemoglobin (Hb) differences.

		N	Subset for alpha = .05	
		1	2	1
Group	Transamin	30	1,6833	
	Adrenalin	30		2,3067
	Control	30		2,6700
	Sig.		1,000	,208

Haemoglobin DIFFERENCES
Tukey HSD.

After surgery, 9 units of RBC suspensions were administered to 5(17%) patients in Group 3. Three (10%) patients received a total of 4 units of RBC suspensions in Group 2, while no transfusion was needed for any patient in Group 1 (Figure).

No complications, such as infection, pulmonary emboli

Table-2: An overview of haemoglobin, haematocrit levels and volume of drainage in three groups.

Variable		Groups			p Value
		I	II	III	
Preoperative	Haemoglobin (g/dl)	13.07±1.41	13.29±1.18	13.53±1.45	0.44
	Haematocrit	39.46±4.07	39.88±3.40	40.63±4.10	0.50
Postoperative 6th hour	Haemoglobin (g/dl)	12.48±1.37	12.57±1.16	12.49±1.29	0.96
	Haematocrit	37.53±4.03	37.44±3.29	37.39±3.59	0.99
Postoperative 24th hour	Haemoglobin (g/dl)	11.39±1.25	10.98±1.26	10.86±1.34	0.24
	Haematocrit	33.77±3.76	32.44±3.40	32.25±3.84	0.22
Δ Haemoglobin		1.68±0.79	2.30±0.78	2.67±0.90	<0.001*
Δ Haematocrit		5.69±2.32	7.44±2.85	8.37±3.03	0.001*
Drainage (ml)		321.67±172.05	615.00±225.58	800.00±248.10	<0.001*

(Statistically significant; Group I: TXA; Group II: adrenaline; Group III: control; Δ Haemoglobin: difference between haemoglobin levels initially and on 24th hour postoperatively; Δ Haematocrit: difference between haematocrit levels initially and on 24th hour postoperatively).

Analysis of variance (ANOVA) is used to compare the group's means. If the mean difference between groups are significant, then Tukey test is performed and the results are given in Table 3 and Table 4. After ANOVA analysis, differences between groups are significant in that Δ Haemoglobin, Δ Haematocrit and Drainage. The Tukey multiple test results the source of difference are detected. The Tukey results are given in Tables 3-5.

Table-5: Statistical evaluation of haematocrit differences.

		N	Subset for alpha = .05	
		1	2	1
Group	Transamin	30	5,6867	
	Adrenalin	30		7,4400
	Control	30		8,3733
	Sig.		1,000	,392

Haematocrit (HCT) DIFFERENCES
Tukey HSD .

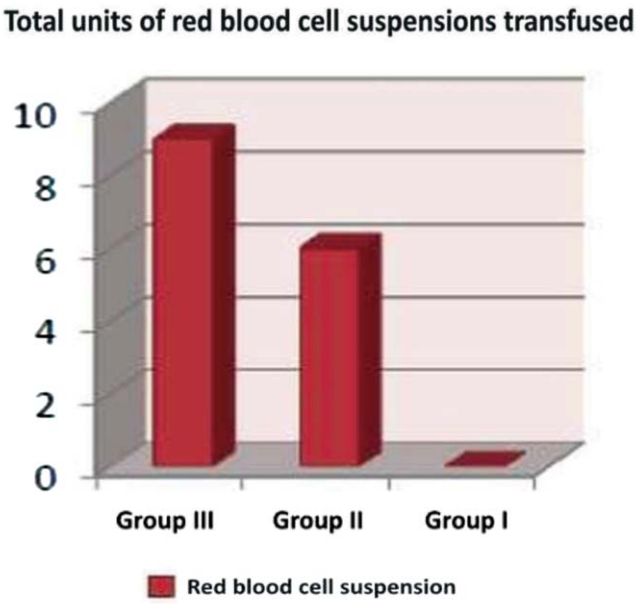

Figure: The amount of red blood cell suspensions transfused in three groups.

and DVT, were detected in any patient.

Discussion

TKA is an effective treatment for osteoarthritis of the knee, but this surgery is frequently accompanied by severe blood loss. The amount of blood loss for TKA varies between 500 and 1.500ml[17] In spite of the development in surgical techniques and perioperative care, TKA is still associated with substantial bleeding. Since considerable bleeding can increase morbidity, many methods have been proposed to reduce perioperative blood loss and preserve haemodynamic stability in patients undergoing TKA. In this regard, topical agents such as TXA, adrenaline and other haemostatic gels and powders have been recommended. Even though these methods have reduced the need for allogeneic blood transfusion (ABT), none of them alone has been enough.[18] The most obvious finding of the current study is that topical TXA can be effective in managing postoperative blood loss and may avoid the need for ABT after TKA.

A study demonstrated that topical TXA can be very effective in managing postoperative blood loss, and avoiding ABT in primary TKA. When adrenaline was added to the TXA saline solution, there was a greater haemostatic effect compared to the TXA saline solution alone.[11] In the present study, we compared the haemostatic effects of adrenaline and TXA separately and noted that TXA had a more prominent impact on controlling blood loss after TKA.

TXA is an inhibitor of fibrinolysis and an activator of plasminogen and is known to inhibit blood loss after TKA.[19] Since TKA is mostly performed under tourniquet, veins of the lower extremity are in a hypoxic state, and this may lead to the release of tissue plasminogen activator from the vascular endothelium. Tourniquet deflation results in venous expansion and increased haemorrhage in the lower extremity. Fibrinolysisis temporarily activated after surgery and bleeding will be aggravated. TXA strongly blocks the fibrinolysis and promotes the stability and deposition of blood clots in the tissue space.[11] The haemostatic effect of adrenaline is linked with the peak of blood flow which persists for 20-30 minutes following the release of tourniquet release. Local adrenaline infusion prior to the release of the tourniquet not only triggers contraction of peripheral vessels, but also induces platelet aggregation. Therefore, adrenaline can be useful for peripheral vessels and haemostatic effect of reducing perioperative and postoperative blood loss.[15]

In accordance with the results of a previous publication,[11] we observed that IA use of TXA and adrenaline solutions with drainage started 30 minutes after surgical closure of the wound were safe without any apparent postoperative complications such as DVT and pulmonary emboli. Notably, there was no need for transfusion of RBC suspension for patients receiving TXA.

In conjunction with data from the relevant literature[20,21] our results support that use of TXA in the articular cavity provided the satisfactory haemostatic effect. Meta-analyses indicated that TXA remarkably reduced both the number of patients requiring transfusion and volume of blood products transfused.[22]

Even though it has been suggested that intra-articular adrenaline injection was effective for decreasing blood loss in TKA[23] a study reported that it was not useful.[24] Our results indicated that even though TXA had a more obvious effect than adrenaline for haemostasis after TKA. However, we think that adrenaline may be used as an adjunctive measure to enhance the activity of TXA.

Main limitation of the current study is its retrospective design and single-institution orientation. Possible complications and adverse events can be investigated

more accurately in larger series. Lack of analysis of the synergistic effects of TXA and adrenaline is another significant limitation. Moreover, we recruited only patients with osteoarthritis of the knee alone, without other inflammatory disorders such as rheumatoid arthritis. Hence, interpretation and extrapolation of our results must be made with caution. Our data may be restricted since there is no long-term follow-up and diagnosis of DVT was based on clinical presentation only.

Depending on the selection of the surgeon and characteristics of the patient, TXA may be administered intravenously or topically in the surgical wound.[18] The optimal treatment protocol for TXA remains to be determined in further studies. A study stated that IV TXA was more effective than local application due to the decreased absorption.[25] However, IA administration after surgical closure of the capsule can be a method to overcome this problem.

Conclusion

TXA was beneficial for the reduction of total blood loss, postoperative blood loss, Hb loss, the units of blood products transfused per patient and the number of patients receiving blood transfusions after TKA. Both TXA and adrenaline did not seem to increase the risk of thromboembolic complications and other adverse events.

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Conflict Interest: None.

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