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A prospective comparative study between intravenous and intraarticular tranexamic acid administration in decreasing the perioperative blood loss in total knee arthroplasty

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ABSTRACT

Purpose: Total knee arthroplasty (TKA) is a common and safe surgical procedure, but the high perioperative blood loss is a cause of concern. Use of tranexamic acid to address this issue has gained popularity recently but no clear consensus is available regarding its ideal mode of administration. We conducted this study to evaluate and compare the efficacy of intravenous as well as intraarticular routes of administration of tranexamic acid.

Methods: 300 patients planned for B/L Total Knee Arthroplasty were randomized into 3 groups; group IV (Intravenous, n = 100), group IA (Intraarticular, n = 100) and a control group (n = 100). In group IV, patients received 1 g tranexamic acid intravenously; in group IA 2.5 g tranexamic acid was given intraarticular in both knees and a control group which did not receive tranexamic acid. The primary outcomes measures were total blood loss (intraoperative blood loss + drain amount), pre and post surgery haemoglobin levels and the transfusion rate and quantity. The secondary outcome measures were complications.

Results: Administration of tranexamic acid through either of the two routes resulted in statistically significant decrease in the total perioperative blood loss and transfusion requirement. There was no statistically significant difference in the results between the two test groups.

Conclusions: Both intravenous as well as intraarticular administration of tranexamic acid provided excellent results no known adverse effects. However neither of the two modalities should be considered superior to the other.

1. Introduction

Total knee arthroplasty (TKA) is a common surgical procedure performed to relieve the pain and disability associated with advanced arthritis of the knee due to any cause. The dramatic improvement in pain and functional status of the patient has lead to its widespread acceptance. Although this procedure is considered to be relatively safe, the high perioperative blood loss[1,2] is a cause of concern. Since majority of the patients undergoing a TKA are in the older age group with associated co-morbidities, significant blood loss carries an even greater risk.

In order to address this problem various strategies are available. These include use of pneumatic tourniquet, regional anaesthesia, controlled hypotension, intra-operative blood salvage etc. The use of intra-operative tourniquet to decrease the total blood loss in TKA has remained questionable.[3,4] Despite these measures, the amount of blood loss in TKA ranges from 500 to 1500 ml[5,6] which necessitates the frequent use of allogenic blood transfusion. Excess bleeding may lead to prolonged post-operative pain, wound hematoma formation and arthrofibrosis, all of which may compromise the final outcome of surgery. Hence perioperative blood loss management is imperative to prevent the bleeding related complications and transfusion related morbidity. One such strategy that is gaining popularity worldwide over the last few years is the use of an antifibrinolytic agent such as tranexamic acid.

Various studies including reviews and meta-analysis have demonstrated the efficacy of both intravenous(IV) and

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intraarticular(IA) administration of tranexamic acid in reducing blood loss in TKA without any increased risk of thromboembolic complications.[9–11] However no clear consensus is available regarding which mode of administration is superior. This has prejudiced the use of this potentially valuable substance in becoming a routine in orthopaedic practice.

Hence we conducted this study to evaluate the efficacy as well as compare the two modalities of tranexamic acid administration i.e. intravenous & intraarticular, in reducing the perioperative blood loss and transfusion requirements in patients undergoing total knee arthroplasty. Further the results were compared with a control group in which tranexamic acid was not given with all other factors kept alike.

2. Materials and methods

A prospective comparative study was conducted between April 2016 and Oct 2017 involving 300 consecutive patients scheduled for total knee arthroplasty due to advanced osteoarthritis of knee. Only cases undergoing Bilateral Total Knee Arthroplasty were included in our study to maintain uniformity.

Each patient scheduled for a primary B/L TKA in our centre was subjected to a thorough evaluation. The pre-operative haemostatic assessment including haemoglobin level, platelet count, bleeding time, clotting time, Prothrombin time, activated partial thromboplastin time, INR ratio was done apart from other routine investigations.

Patients with history of previous ipsilateral knee surgery, allergy/hypersensitivity to TXA, known history of thromboembolic disease (DVT/PE/Stroke/transient Ischemic attack), any renal/hepatic insufficiency or preoperative coagulopathy (platelet count<150000/INR>1.4) were excluded.

The study was approved by the institutional ethics committee. A written informed consent was taken from the patients who fulfilled the criteria. The base line characteristics of the patients such as age, weight, height, BMI, gender and any co-morbidity were recorded.

Patients were subjected to computer generated randomization and were allocated to an Intravenous (**IV**) group (n = 100), an intraarticular (**IA**) group (n = 100) and a control(**C**) group (n = 100).

In Group IV, patients received 1 g tranexamic acid through intravenous route after sensitivity testing. TXA was administered after combined spinal epidural anaesthesia was given but before inflation of tourniquet. A single dose of tranexamic acid was given in our study.

In Group IA, patients received 2.5 g TXA (500mg/5 ml vial; 25 ml) diluted with 25 ml normal saline to form a total volume of 50 ml given equally in both the knee joints after wound closure through the drain pipe which was clamped immediately after administration of TXA.

In Group C patients did not receive tranexamic acid with all other factors kept alike.

2.1. Operative technique and post operative care

Bilateral Total Knee Arthroplasty was performed under combined spinal epidural anaesthesia. The same surgical team operated all the cases. The pneumatic tourniquet was applied to the proximal thigh with pressure of 280 mm Hg. Prophylactic antibiotics were given and the standard midline skin incision and medial parapatellar arthrotomy approach was used. After bony preparation, the implant (PFC sigma, DePuy) was inserted with full cementation. The orifice of the femoral medullary cavity was plugged with a bone fragment. Post cement setting the tourniquet was deflated and bleeders were cauterised. The intraoperative blood loss was determined by measuring the weight change of gauze pieces/mop pads by using a weight measuring device and by observing the fluid level of suction reservoirs. From the sum of these two values the volume of fluid used for irrigation was subtracted which gave us an approximate value of the intraoperative blood loss. The standard drain tube (Size 14) was placed in the joint. Wound was closed sequentially in layers. As mentioned above, in Group IA, the tranexamic acid preparation was injected into the joint using the drain and immediately clamped. A bulky compressive dressing was applied thereafter. In all patients the drain was clamped for 4 h and then opened. The drain was removed at the time of 1st post op dressing done on day 2 of surgery.

In the post operative period each patient received the same protocol regarding analgesia, antibiotic prophylaxis and DVT prophylaxis. We use tablet apixaban 2.5 mg started 24 h after surgery and given twice a day for 12 days for DVT prophylaxis. The post operative Hb level was assessed on day 2 and this value was used for comparison in our study. Blood transfusion was done if Hb level was less than 10 or if any anaemic symptoms or anaemia related organ dysfunction was suspected and this was recorded.

The drain output was measured and recorded at the time of removal of drains on post op day-2. Patients were encouraged to do ankle pump exercises in the immediate post op period and were mobilised using walker on day 2 of surgery. Patients were daily assessed clinically for any signs of DVT/PE and Doppler ultrasound was done only if any symptoms suggestive of DVT were present. Any other post op complications such as skin necrosis, infection etc were also recorded.

2.2. Outcome measures

The primary outcome measures included the total amount of blood loss (intraoperative blood loss + post operative blood loss through suction drains of both knees), the pre and post surgery haemoglobin levels, the transfusion rate and the transfusion quantity. The secondary outcome measures were complications such as superficial or deep infection, wound dehiscence, DVT, Pulmonary embolism, or any organ dysfunction.

2.3. Statistical analysis

Statistical analysis was performed by the SPSS program for Windows, version 17.0. Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis using Shaipro Wilk test. Normally distributed continuous variables were compared using ANOVA. If the F value was significant and variance was homogeneous, Tukey multiple comparison test was used to assess the differences between the individual groups; otherwise, Tamhane's T2 test was used. Categorical variables were analyzed using the chi square test. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

3. Results

The demographic data of the three groups was comparable with no significant differences in age, weight, height, BMI and gender distribution (Table 1).

The operative and post operative characteristics are presented in Table 2. The mean value of the tourniquet time did not show any significant difference ($p = 0.585$) between the three groups. The Hb values preoperatively varied from 10.8 to 14.9 but the mean values in all groups were comparable. The post op Hb values were significantly lower in the control group and the fall of Hb was significant when compared between the Control and IV group as

Table 1
Demographic factors.

	Control Group	Group IV	Group 1A	P Value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age	61.34 ± 7.38	62.86 ± 6.08	61.85 ± 4.81	0.219
Weight	64.25 ± 11.08	65.61 ± 12.02	62.83 ± 11.37	0.234
Height	1.55 ± 0.13	1.58 ± 0.09	1.57 ± 0.09	0.084
BMI	27.36 ± 6.12	26.52 ± 5.58	25.79 ± 5.04	0.143
Gender(F/M)	62/38	59/41	56/44	0.689

Table 3
Transfusion data.

Transfusion	Control Group	Group IV	Group 1A	P Value
	Frequency (%)	Frequency (%)	Frequency (%)	
0	26 (26.0%)	63 (63.0%)	56 (56.0%)	<0.001
1	56 (56.0%)	32 (32.0%)	27 (26.0%)	
2	17 (17.0%)	5 (5.0%)	10 (10.0%)	
3	1 (1.0%)	0 (0.0%)	0 (0.0%)	
Total	100 (100%)	100 (100%)	100 (100%)	

well as between the control and the IA group ($p = 0.013$). However no such statistically significant difference existed when the values were compared between the two test groups i.e. the intravenous and intraarticular group ($p = 1.0$).

The intraoperative blood loss values declined maximally in the IV group and the result was statistically significant ($p < 0.001$). This shows that there is a significant reduction in intraoperative blood loss when intravenous tranexamic acid is given at the start of the surgery. Since IA tranexamic acid is given through drain pipes after wound closure, its main role is to decrease the volume of post operative blood loss through suction drains.

The mean total drain output in each of the two test groups was much lower than the control group. The results were statistically significant in all intra group comparisons thereby implying that the extent of post operative blood loss in significantly reduced in both the test groups as compared to the control group and this reduction was more in the IA group as compared to the IV group.

The mean total blood loss of both knees in the control group was 1061.30 ± 170.06 whereas in the IV and IA groups it was 607.90 ± 94.37 and 614.15 ± 128.73 respectively. Both test groups had a statistically significant reduction in the total blood loss. However we could not find any statistical difference between the two test groups ($p = 0.972$).

The transfusion rate in control group, IV group and IA group was 74%, 37% and 44% respectively. The number of units transfused was also higher in the control group with respect to the two test groups and this difference was statistically significant (Table 3).

3.1. Complications

In our study no adverse events attributable to tranexamic acid were found in any of the patients receiving either IV or IA tranexamic acid. One patient in the control group developed deep infection which was managed as per protocol. 3 patients in IV and 2 in IA group developed superficial stitch line infections which were managed by debridement and extended course of antibiotics. No patient was found with signs of DVT or pulmonary embolism.

4. Discussion

Total knee arthroplasty is becoming increasingly popular primarily due to its high success rate and minimal complications. Perioperative blood loss management has been identified as the key factor that can further improve the outcome of this surgery. Out of the various strategies that are available, tranexamic acid has shown promising results in various studies done in recent years to evaluate its efficacy and safety profile.[9–11]

In the present study, the role of tranexamic acid, given by two most popular routes of administration i.e. the intravenous route and the intraarticular route, was investigated in cases of B/L TKA. This was done by monitoring a variety of parameters such as the drop in haemoglobin levels, the difference in the intraoperative blood loss, drain amount and transfusion requirements between the two test groups and further the results were compared with a control group to validate the findings.

For intravenous administration of TXA, no clear cut guidelines are available in literature regarding the dosage, number of injections and time of administration of tranexamic acid. Various authors have reported excellent results with multiple dose IV administration regimes involving 2–3 doses given at specified times during the surgery ranging from just before tourniquet inflation till 3 h after surgery.[9,10,12,13] Tzatzairis T et al.[15] conducted a study comparing the role of IV TXA with topical TXA in decreasing blood loss in TKA found that a single 1 g IV TXA administration given 20 min before tourniquet inflation was effective in decreasing the blood loss. However conflicting evidence was provided by other authors such as Maniar RN et al.[18] who found that a single dose did not give effective results and the three dose regime gave best results. Regarding the amount of TXA, Noticewala MS et al.[16] reported good results with 500 mg IV tranexamic acid, but most authors have used a dose of 10 mg/kg[9,10,12,13] or a fixed dose of 1 g[14,15] TXA. We used a single dose of 1 g tranexamic acid given 15–20 min prior to tourniquet inflation in our study.

Regarding topical administration also no fixed guideline is available in current literature. Multiple studies[9–16] using different

Table 2
Operative and post operative characteristic and comparisons.

Tourniquet time (minutes)	Control Group	Group IV	Group 1A	P Value	Control Group V/S Group IV	Control Group V/S Group 1A	Group IV V/S Group 1A
	Mean ± SD	Mean ± SD	Mean ± SD				
	85.96 ± 8.20	86.26 ± 8.83	85.00 ± 9.83	0.585			
Haemoglobin (g/dl)							
Pre op	12.85 ± 0.97	12.74 ± 1.01	12.76 ± 1.11	0.712	0.727	0.788	0.994
Post op	9.96 ± 1.12	10.41 ± 1.00	10.41 ± 1.17	0.005	0.013	0.013	1.000
Drain output (ml)							
Right	366 ± 11.66	219.5 ± 60.09	156.35 ± 58.09	<0.001	<0.001	<0.001	<0.001
Left	363 ± 102.4	222.6 ± 54.84	180 ± 63.04	<0.001	<0.001	<0.001	<0.001
Total	729 ± 156.38	442.1 ± 19.73	336.35 ± 89.95	<0.001	<0.001	<0.001	<0.001
Intraoperative blood loss(ml)	332.30 ± 64.71	165.80 ± 49.75	317.80 ± 86.15	<0.001	<0.001	0.1799	<0.001
Total blood loss(ml)	1061.30 ± 170.06	607.90 ± 94.37	614.15 ± 128.73	<0.001	<0.001	<0.001	0.972

concentrations of tranexamic acid for local administration have been published showing good results. Concentrations of TXA ranging from 1 g to 3 g diluted with normal saline have been used in these studies. Most have administered the diluted tranexamic acid solution through the drain pipe into the joint cavity after wound closure. In the present study, good results were obtained with diluted solution of 2.5 g TXA administered in both knees intraarticularly. The drain pipe was clamped immediately and opened after 4 h because for the agent to work a stipulated contact period is necessary. The duration of clamping the drain pipe was variable in the literature with the usual duration being 1 h.[16] Paphon Sa-ngasoongsong et al.[17] evaluated the efficacy of low dose IA-TXA with prolonged drain clamping (upto 12 h) and found it to a safe and effective blood conservation technique. The proposed advantage of intraarticular mode of administration is that since the systemic absorption is very low[17] the theoretical adverse effects of TXA, such as increased risk of thromboembolic events, can be minimised by using this approach.

Despite the abundance of literature supporting the use of tranexamic acid in reducing blood loss associated with TKA, its routine use is still limited and this was the key reason why we conducted this study. In the present study, it was found that IV administration of TXA was effective in decreasing both the intra operative blood loss as well as the drain amount, effectively decreasing the mean perioperative blood loss by over 40%. As a result the transfusion requirement in this set of patients also went down.

Since the surgeries were performed under tourniquet control, we were sceptical about the raised risk of thromboembolic events due to TXA usage. However this group did not have any thromboembolic complications or any other adverse events which may be attributed to the use of IV tranexamic acid.

Similar results were obtained in Group IA, in which intraarticular administration of TXA acid was done. Significant decrease in the drain output was observed, as a result of this, fall of Hb and the transfusion requirement went down in this group of patients. No adverse local events were reported following the use of TXA in the joint cavity.

These finding are in accordance with the existing literature with minor differences.[9–16] We feel the differences are due to the different regimes and the dosage of TXA used in other studies as a higher dose could lead to better haemostasis.

In the present study bias was eliminated by including a demographically comparable population, with the surgery performed by the same surgical team using a fixed implant design. However, we feel that there were several shortcomings of our study. Firstly, we recognise that our study was not blinded. Secondly the role of different concentrations/repetition of TXA could not be investigated because of lack of dose dependant groups. Also the long term sequelae of its use or development of any late thromboembolic events was not studied.

The results of our study further reinforce the fact that tranexamic acid is an extremely valuable agent that is cheap, easily available and devoid of any adverse effects, that may have a tremendous role to play in improving the outcome of TKA surgeries in the future.

5. Conclusions

In our study involving 300 subjects undergoing B/L Total Knee Arthroplasty, we found that a single preoperative dose of 1 g tranexamic acid is highly effective in decreasing the perioperative blood loss with no known adverse effects. The intraarticular administration of tranexamic acid also provided similar results. The use of this cost effective measure to conserve blood is thus recommended. But we also conclude that neither of the two modalities should be considered superior to the other as both have shown similar results. Further clinical studies are necessary to determine the precise dosage and timing to make the best use of this worthy agent.

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[7, 8].

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