Tranexamic acid in primary total knee arthroplasty: ideal route of administration

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Abstract

Background & Study Aims: Consensus is lacking regarding the optimal route and dose of administration of Tranexamic acid (TXA) so this study was conducted to compare the efficacy and safety of topical, oral and intravenous routes (iv) of TXA with routine hemostasis alone in patients undergoing primary total knee arthroplasty (TKA).

Materials and methods: A prospective randomized trial was conducted in patients undergoing primary TKA. Patients were divided into four groups of 50 each; group 1 received intraarticular TXA, group 2 received oral TXA three hours before surgery, group 3 received IV TXA just before tourniquet release and group 4 did not receive TXA. Post-operative drain volume (PODV), fall in haemoglobin (Hb) level and the required amount of blood transfusion were evaluated.

Results: PODV and drop in Hb level respectively were (158 ± 90 ml and 1 ± 0.5 g/dl) in group 1, (328 ± 149 ml and 1.7 ± 0.7 g/dl) in group 2, (311 ± 151 ml and 2.1 ± 1 g/dl) in group 3 and (589 ± 115 ml and 3.2 ± 1.2 g/dl) in group 4. The difference in drain volume between all groups was statistically significant except between groups 2 and 3. Transfusion requirements were significantly greater in group 4 ($p < 0.001$).

Conclusions: Intra-articular, oral and IV TXA were observed to be safe strategies and more effective than tamponade effect alone to reduce drain volume and transfusion requirements after TKA. Additionally, intra-articular TXA was better than oral or IV TXA with respect to drain volume and post-op drop in Hb.

Keywords: total knee arthroplasty; tranexamic acid; intra-articular; oral; intravenous

Introduction

Total knee arthroplasty (TKA) is one of the most commonly performed elective orthopaedic procedures. Wherever indicated, it provides significant pain relief and improvement in the quality of life. Leg swelling, post-operative pain and blood loss are some of the frequent problems following TKA which may compromise the rehabilitation process. Considerable blood loss after TKA is most problematic, requiring significant post-op blood transfusion (BT) which carries a substantial risk of both immunologic reaction and transmission of diseases. Per-operative blood loss is largely restricted during the procedure by the use of a tourniquet. Post-op blood loss accounts for a major component of

total blood loss and most of it occurs during the initial post-op period (24 hours).[1] While the risks of non-transfusion offset those of transfusion-related complications; associated costs, shortage of matched blood products and ineffectiveness of shed autologous blood re-transfusion justify investigating efforts to find new blood conserving methods.[2,3]

Although tranexamic acid (TXA) has been used for over 20 years in surgical practice as an agent to control blood loss on account of its fibrin clot stabilizing property; surgeons have hesitated to use it routinely due to insufficient evidence of its efficacy versus the unresolved issue of possible thromboembolic events.[4,5] It has also been shown to have anti-inflammatory properties that might help in early rehabilitation.[6] The best mode of TXA administration for patients undergoing TKA is not clear.[7] Due to safety concerns with systemic administration of TXA, there has been a growing interest in the intra-articular/ topical use of TXA for curtailing blood loss in orthopaedics. Since intra-articular instillation of TXA can directly target the source of bleeding, it can be considered to be a safer method of delivery while decreasing potential systemic effects, even in hemophilic patients.[8] Other drugs like carbazochrome sodium sulfonate have been used alone or in conjunction with TXA to good effect.[9]

The current study was conducted to determine the best possible route of administration of TXA in patients undergoing TKA to minimize post-op blood loss.

Materials and methods

This study was carried out in our department on two hundred patients after approval from the institutional ethics committee [IEC/Th/17/ Ortho2 (Dated 20/3/17)]. Written informed consent was taken from every patient before surgery. The inclusion criteria were primary osteoarthritis of the knee, no previous surgery in that limb and age group of between 40 to 80 years while the exclusion criteria included bleeding disorder, previous history of adverse drug reaction or allergy to TXA, hepatic, cardio-respiratory or renal insufficiency (serum creatinine >1.5 mg/dl) and recent history of thromboembolic episode.

The patients were divided into four groups of 50 each. Group 1 received 1.5 g intra-articular TXA, Group 2 received 1.95 g of TXA (3 tablets of 650 mg each) with a sip of water three hours before incision, group 3 received 1.5 g IV TXA just before tourniquet release while group 4 did not receive any TXA.

All preoperative medications containing salicylates and NSAID were stopped a week preceding surgery. Pre-operative haematological investigations like Haemoglobin (Hb) and coagulation profile were carried out in all cases.

All surgeries were done under combined spinal-epidural anaesthesia and pneumatic tourniquet. After thorough cleaning and draping, exsanguination of the affected limb was done through elevation for two minutes.

Tourniquet cuff pressure was set to 300 mmHg. A standard medial parapatellar approach with anterior midline incision was used in all the cases. A posterior stabilized cemented knee prosthesis (Stryker, USA) was used in all the patients. No patellar resurfacing was done in any case but was managed by osteophyte removal and cauterization of margins all around the patella. After achieving hemostasis, the wound was closed in layers over a negative suction drain. Tourniquet was deflated after the application of pressure bandage.

In group 1, 1.5 g of TXA diluted in normal saline (NS) to make 50 ml was instilled

	Group 1 (n= 50)	Group 2 (n= 50)	Group 3 (n= 50)	Group 4 (n= 50)
Age	59.2 ± 7	60.7 ± 8.5	59.1 ± 9.2	61.4 ± 8.5
Female	40 (80%)	40 (80%)	36 (72%)	47 (94%)
Male	10 (20%)	10 (20%)	14 (28%)	3 (6%)
Bilateral	2 (4%)	4 (8%)	0	0
Left	22 (44%)	28 (56%)	26 (52%)	22 (44%)
Right	26 (52%)	18 (36%)	24 (48%)	28 (56%)

Table 1. Age, Sex and Side descriptive

through the drain tube while in groups 2, 3 and 4, only 50 ml of NS without TXA was used and the drain was clamped for two hours postoperatively in all patients. The drain was removed after 48 hours of surgery or stoppage of the drain column whichever was later and drain volume was noted. The Hb level at 3rd, 4th and 5th day after surgery was checked and the least of the three values were taken into consideration. Final drain volume and blood transfusions were noted. BT was considered if post-op Hb reduced to ≤ 8.5 g% or drain collection of ≥ 500 ml (possible ongoing loss) in the first 8-10 hours or pre to post-op Hb drop of ≥ 4 g%.[10]

Standard post-op care was provided. Quadriceps strengthening exercises and ankle pumps were started on the same evening. The limb was kept elevated on a pillow. Knee bending exercises were started as and when the patient was comfortable. No chemoprophylaxis for deep vein thrombosis was used.

Post-op assessment was done at 1, 2, 3 and 6 months as per the modified Hospital for Special Surgery Knee Scoring System (HSS).[11] All the patients completed the study period and were finally evaluated at 6 months follow up. Any adverse effect from patient admission to final follow up was noted.

Microsoft Excel (2019) spreadsheet and R software for Windows (version 3.6.1) were used. Quantitative data were presented as mean and standard deviation whereas qualitative data were presented as ratio and proportions. ANOVA test was used for detecting the difference between continuous variables that were normally distributed.

	Group 1	Group 2	Group 3	Group 4	*p-value
Drain volume (ml)	158 ± 90	328 ± 149	311 ± 151	589 ± 115	p <0.001 (All comparison significant, except group 2 vs 3)

Table 2. Drain volume (*Kruskal Wallis Test)

	Group 1	Group 2	Group 3	Group 4
Pre-op Hb (g%)	11.9 ± 1.2	11.7 ± 1.2	12.9 ± 1.3	12.5 ± 0.9
Post-op Hb (g%)	10.9 ± 1.1	10 ± 1	10.8 ± 1.1	9.3 ± 1.5
Decrease in Hb (g%)	1 ± 0.5	1.7 ± 0.7	2.1 ± 1	3.2 ± 1.2

p <0.001 (All comparisons significant except group 2 vs 3) (ANOVA test)

Table 3. Pre-op, post-op and fall in Hb

Kruskal Wallis Test was used to analyze the drain volume. A chi-square test was used to check the association between qualitative variables. The point of statistically significant difference was considered when $p < 0.05$.

Results

All the four groups were comparable in terms of age, gender distribution, body mass index, laterality, other demographic and clinical variables, tourniquet time and duration of surgery ($p > 0.2$). Most of the patients were female. *(Table 1)*

The 48 hours drain volume was significantly lesser in all the TXA groups as compared to the control group ($p < 0.001$). The decrease in drain volume was more significant in group 1 as compared to groups 2 and 3 ($p < 0.001$). *(Table 2)*

The mean fall in Hb was maximum in group 4 and least in group 1. The difference was also significant between group 1 and groups 2 and 3 ($p < 0.001$). *(Table 3)*

The incidence of post-op BT was maximum in group 4. Sixty-two patients required BT of which 45 (73%) patients were from group 4 while 5 patients were from group 1 and 6 patients each from groups 2 and 3 (Table IV). There was no statistical difference between the TXA groups.

The pre-operative functional outcome scores were comparable among all the four groups; however, the post-op functional outcome scores were significant between groups 1, 2 and 3 vs group 4 at 1st and 2nd-month follow-ups. *(Table 5)*

While there was a significant improvement in HSS scores at 1st and 2nd month follow up ($p < 0.005$), it was better in TXA groups as compared to the control group. However, at the time of final evaluation at 6 months, the HSS score was comparable in all the groups.

No. of Blood units transfused	Group 1 (n= 50)	Group 2 (n= 50)	Group 3 (n= 50)	Group 4 (n= 50)
0	45 (90%)	44 (88%)	44 (88%)	5 (10%)
1	4 (8%)	6 (12%)	6 (12%)	28 (56%)
2	1 (2%)	0	0	17 (34%)

Chi-square, p < 0.001, All comparisons significant (<0.001) except group 1 vs 2, 1 vs 3, 2 vs 3 (p > 0.1)

Table 4. Requirement of blood transfusion

Modified HSS score	Group 1	Group 2	Group 3	Group 4
Pre-op	19.4 ± 4.7	20.2 ± 5	18.7 ± 9.3	17.3 ± 4.6
1 month	50.2 ± 1.6	48.8 ± 0.7	51.6 ± 6.8	45 ± 3
2 months	62.0 ± 2.9	62.2 ± 3.5	66.7 ± 8.7	54 ± 3.5
3 months	79.7 ± 4	79.4 ± 6	81.6 ± 5.8	76.6 ± 5.6
6 months	90.2 ± 3.5	91.5 ± 3.3	92.7 ± 4.7	91.6 ± 2.4

Table 5. Modified HSS knee score (ANOVA)

All the patients were followed up for 2 years to ensure they did not develop complications. Three, five, two and six patients respectively in groups 1, 2, 3 & 4 were lost to followup (all after 7 months).

Discussion

Blood loss is a significant factor in peri-op morbidity following TKA. Reducing it, therefore, is an important objective. A variety of measures have been advocated to minimize the peri-op blood loss like the use of tourniquet, intra-op hemostasis, post-op pressure bandage and various medications.

TXA is widely used in many situations, including trauma, to reduce blood loss and prevent consequent morbidity and mortality. In the recent past, TXA has also been a subject matter of research for reducing blood loss in joint replacement surgeries, especially involving hip and knee. As an antifibrinolytic drug, it counteracts the marked local fibrinolysis associated with the release of the tourniquet which is believed to be the reason for reduced blood loss. There is no consensus as yet on a universally acceptable route of administration (intra-articular, oral or IV), dosage or administration schedule.

Therefore, the present study on 200 patients was conducted to identify the most effective regimen of TXA by comparing drain loss, post-op fall in Hb and requirement of blood transfusion (BT) among the three mentioned methods of administration of TXA with a control group (no TXA). To ensure all patients were comparable with respect to drain volume, in group 1, 1.5 g TXA diluted in NS to make (a volume of) 50 ml, was instilled into the knee through the drain while 50 ml NS was instilled in rest of the groups (oral, IV and control) to equate the tamponade effect.

Final drain volume was 158 ± 90 ml, 328 ± 149 ml, 311 ± 151 ml and 589 ± 115 ml in groups 1, 2, 3 and 4 respectively. The difference was significant between all TXA groups and the control group ($p < 0.001$). Moreover, intra-articular TXA was observed to have an advantage over oral and IV TXA routes ($p < 0.001$) in this regard. Similar studies using intra-articular TXA conducted by Aggarwal et al, Ishida et al, Paphon et al, Camerasa et al and Jansen et al observed a mean drain volume of 168 ml, 210 ml, 309 ml, 787 ml and 678 ml respectively.[12–16] The difference in values of Ishida et al and Paphon et al study can be attributed to reduced dosage strength and volume of intra-articular TXA used (200 mg/20 ml NS and 250 mg/20 ml NS respectively as compared to the present study where a dose of 1.5 g/50 ml NS was used).[13-14]

In a similarly sized study, Zhang et al observed that patients injected with intra-articular TXA

as well as peri-articular TXA had a median drain volume of 57 ml. This could be due to the dual injection and longer contact period in their study of 4 hours as well as drain removal after just one day.[17]

Maniar et al reported a larger drain volume of 385 ml in their study on intra-articular TXA, even though TXA was used in a higher dose (3 g/ 100 ml NS) than our study (158 ml, 1.5 g & 50 ml respectively). This may be however due to lesser contact period of the drug in their study (applied locally on the wound surface after cementing the implant and before tourniquet release for a contact period of only 5 minutes).[18]

Sehat et al in their study observed that following TKA only the final drain volume (measured visible blood loss) is usually known and this underestimates the true total loss, as some loss is hidden.[19] To account for hidden blood loss besides what was apparent in drain volume, post-op fall in Hb was also taken into consideration in the present study. It was presumed that blood volume would reach pre-op level by 3rd post-op day, even then, least of post-op Hb level on 3rd, 4th and 5th day was taken to further eliminate any chance of error. The fall in Hb was maximum in group 4 while among TXA groups it was higher in group 2 and 3 as compared to group 1 [3.2 ± 1.2 g%, 1.7 ± 0.7 g%, 2 ± 1 g% and 1 ± 0.5 g% respectively] ($p < 0.001$). As a result, there was a minimal requirement in post-op BT in the TXA groups following TKA. While most of the patients in the control group met the criteria for transfusion trigger thereby resulting in one or more units of BT (45 out of 50 patients), the requirement in TXA groups was negligible (17 out of 150 patients). Out of these few patients requiring post-op BT in TXA groups, almost all of them were on account of either one or two-stage bilateral TKA, or due to the patient having a pre-op Hb of 10 g%. There were no adverse effects in any of the patients despite not giving any DVT chemoprophylaxis.

While there was a significant improvement in HSS scores at follow up ($p < 0.005$), it was better in TXA groups in the initial months as compared to the control group, similar to the findings of Hirose et al, probably due to its anti-inflammatory action.[6,20]

The limitations of our study included a relatively small sample size and no double-blinding in the study. A further possibility of some of the intra-articular TXA getting absorbed into the systemic circulation cannot be ruled out.

Conclusion

The present study confirms the effectiveness of TXA administration by any route (intra-articular/ oral/ IV) in the reduction of postoperative blood loss following primary TKA without any adverse effects. Further, it also indicates that intra-articular TXA in the dosage prescribed is the most effective route of administration as compared to oral or IV administration.

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