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Is Intraarticular Administration of Tranexamic Acid Better than Its Intravenous Administration in Reducing Blood loss after total Knee Arthroplasty?

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Abstract
Context: *Intravenous (IV) tranexamic acid (TXA) is a goodpotent agent in controlling postoperative blood loss following total knee arthroplasty (TKA). Recently, intraarticular usage of this agent has also shown good results.*
Aims: *Comparison of postoperative blood loss between IV(intravenous) and topical administration of TXA tranexamic acid in TKAs(total knee arthroplasty)*
Materials and Design: *Eighty-six TKAs on knees were included in ourstudy. Randomization was done, so that in our study 40 TKA received 1 g of IV TXA, while 46 had underwent intraarticular administration of 1 gm of TXA.*
Subjects and Methods: *We have compared the postoperative blood loss by calculating the difference in pre- and postop hemoglobin and the need for blood transfusion for patients .The functional assessment was done on basis of Western Ontario McMaster Osteo-Arthritis Index (WOMAC) scores and complications like postoperative infection, oozing from wound site and thromboembolic manifestations.*
Results: *The blood loss was significantly less in the intraarticular administration group as compared to the IV injection group. The total blood loss, blood transfusion, and drain output was also less but the difference was not significant. The functional assessment (WOMAC) scores were equivocal and so were the complications including thromboembolic manifestations (two cases each of deep vein thrombosis (DVT) .There was no cases of pulmonary embolism (PE)).*
Conclusion: *The intraarticular administration of TXA to prevent postoperative bleeding or blood loss in TKA is a safe and effective alternative to its intravenous usage.*
Keywords: *Intraarticular administration, tranexamic acid, total knee arthroplasty.*

Introduction

Tranexamic acid (TXA) drug and its usage is helpful for arthroplasty surgeons in the recent years to reduce postoperative blood loss, especially in total knee arthroplasty (TKA). Many studies and trials have now proved the efficacy and about safety of this drug. [1],[2],[3],[4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14]. Earlier an intravenous (IV)dose in various doses have been used by many surgeons and their results have been extensively studied. [3],[4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14] Oral TXA has shown to have equal efficacy by Zohar *et al.* [1] Nowadays, there is a increase interest in usage of intraarticular administration

of TXA for TKA. Wong *et al.*, [2] and many others [6],[7],[8] have shown good outcome for intraarticular administration of this drug in TKA. But all of them have compared intraarticular administration of TXA with placebo controls. So that, it is difficult to conclude whether the drug actually acts locally or it gets absorbed systemically and then acts like an IV agent. In order to clear these doubts and to confirm the efficacy of topical administration of this drugtranexamic acid (TXA), we have here donea comparative study between topical and IV administration of TXA in TKAs.

Materials and Methods

This study was conducted for a period of 1 year, from June 2016 to October 2017. The inclusion criteria were all patients undergoing uncompli-cated unilateral TKA for primary osteoarthritis consenting to be a part our study. The exclusion criteria was allergy to TXA, preoperative anaemic patients (hemoglobin less than 11 g/dL in males and less than 10 g/dL for females), history of usage of anticoagulant therapy in the period of 5 days before surgery, coagulopathy (which is determined by the platelet count less than 150,000; international normalized ratio (INR) > 1.4; history of thromboembolic disease), and other comorbidities like renal diseases (creatinine > 1.5 g/dL) and cardiovascular compromise or conditions (New York Heart Association class III or IV). Complicated deformity conditions requiring a stem, wedge, or revision components were not included in our study.

All patients were informed clearly regarding the study that they were going to be a part of, its risks and advantages. At the end of 1 year, 86 patients were included in this study, 40 of them had received IV administration while 46 received topical administration of TXA. An equal dosage of 1 g of TXA was used for both types of administrations.

Same protocol of surgical management was used for both the groups. All the patients were operated under epidural anaesthesia, with 300 Hg pressure oftourniquet control. Normal saline (NS) and dextrose normal saline (DNS) fluids were used as maintenance fluid. All the surgeries were done by one senior surgeon (AP) along with his operating team. Medial parapatellar approach(mid line incision) was used for all the surgeries. Standard techniques were used for intraoperative hemostasis. All knees were implanted with a posterior stabilized (PS) cemented knee (Either Exactech or Zimmer). The tourniquet was released after cementing and careful haemostasis was achieved. Wounds were closed in layers over a 12 gauge suction catheter but the suction catheter was not opened until one hour after the surgery.

Intravenous TXA was administered 10 min before the tourniquet was inflated as an infusion while the intraarticular administration was done by injecting 1 g of TXA mixed with 10 mL of NS in the knee joint after closure of the wounds.

The postoperative protocol were also similar for both of the groups. A standard prophylaxis or prevention against venous thromboembolism in the form of subcutaneous injections of low molecular weight heparin (LMWH; enoxaparin 40 mg) was given to all patients once daily from the first postop day till 7 days of postop. Postop conditions were evaluated by checking daily hemoglobin level for the first 3 days along with packed cell volume (PCV). Drain output measured every 8 hourly and drain tube was removed after 48 hours following nil active draining in the tube. Blood transfusion was necessary only if post op hemoglobin was < 8 mg/dL or even at more than 8 g/dL if the patient developed intolerable symptoms of anemia, not attributable to any other causes recommended by American Society of Anesthesiologists (ASA) task force. [15] One unit of blood transfused at a time, till we got a recovery of hemoglobin above 8, and the tests confirmed it. The total blood loss was calculated using these values the formula prescribed by Good *et al.*, [17] and Nadler *et al.* [20] (Figure 1). Surgical infections, oozing from wound site, and time of stitch removal were noted carefully. Functional evaluation were done using

the Western Ontario McMaster Osteo-Arthritis Index (WOMAC) scores. Diagnostic Doppler ultrasound examination was done for both legs of the patient to evaluate for any deep vein thrombosis (DVT) on pre op and 2nd day post op . All thromoembolic events were noted and recorded till 12 weeks follow-up of the patient.

Formula

$$Hb_{loss} = BV \times (Hb_i - Hb_e) \times 0.001 + Hb_t$$
$$\text{Blood loss} = 1000 \times Hb_{loss}/Hb_i$$

Hb_{loss} is the amount (g) of hemoglobin lost

Hb_i is the hemoglobin level (g/L) before surgery

Hb_e is either the lowest postoperative recording of the hemoglobin level (g/L) or the hemoglobin level (g/L) recorded right before any transfusion

Hb_t is the total amount (g) of hemoglobin transfused

Figure 1: Calculation of postoperative blood loss on the basis of hemoglobin balance according to equations described by Good, et al., and Nadler, et al.

Statistical analysis used

Statistical Package for Social Sciences (SPSS) 18.0 (Windows, NY) was used for all analysis. A student's *t*-test was used to compare the demographics and results of the two groups. *P* of < 0.05 was taken as significant.

Results

Six months was taken as the minimum follow-up for evaluation of these results and all 86 patients were successfully followed up during this period. There was no significant difference in sex, age, body mass index (BMI), preoperative hemoglobin, and INR of the two groups (TABLE 1). Average tourniquet time and surgery time for both the groups was same. The amount of perioperative fluid given was also comparable for both groups (TABLE 1). The preoperative range of motion (ROM), knee flexion, and WOMAC scores were also comparable for both groups.

Table 1: Demographics

	Intraarticular group (*N*=46)	IV group (*N*=40)	Significance (*P*>0.05)
Age	65.6±13.5	65.1±14.1	Not significant
Sex (female/male)	32/14	29/11	Not significant
BMI (kg/m²)	31.5	31.8	Not significant
Average preop Hb (g/dL)	12.8 (10-14.6)	12.9 (10.2-14)	Not significant
Average preop INR	0.97 (0.9-1)	0.97 (0.9-1)	Not significant
	Intraarticular group (*N*=46)	**Intravenous group (*N*=40)**	**Significance (*P*<0.05)**
Average preop ROM (degree)	64 (40-110)	62 (30-120)	Not significant *P*>0.05
Average preop WOMAC score	44 (34-60)	45 (32-60)	Not significant *P*>0.05
Average rourniquet time (min)	72 (65-80)	70 (60-78)	Not significant *P*>0.05
Average surgical time (min)	86 (80-95)	85 (75-95)	Not significant *P*>0.05
Average perioperative fluid (mL)	6,160 (5,900-6,800)	6,220 (6,000-6,900)	Not significant *P*>0.05

IV = Intravenous, BMI = Body mass index, Hb = Hemoglobin, INR = International normalized ratio, ROM = Range of motion, WOMAC = Western Ontario McMaster Osteo-Arthritis Index

Average decrease in hemoglobin was remarkably more for the IV group (average 1.6 g/dL, range 0.8-2.8 g/dL) than the topical administration group (0.9 g/dL, range 0.4-2.0 g/dL) (*P* <0.05, significant). Reduction in blood loss was seen for the topical administration of TXA (average 1,020; range 650-1,550 mL) as compared to the IV group (average 1,205 mL, range 800-1,650 mL) although this was not significant (*P* > 0.05). Rate of blood transfusion was more for the IV group (7/40 (17.5%), total 12 units, 0.3 units/patient, range 0-2) as compared to the topical group (6/46 (13%), total 9 units, 0.2 units/patient, range 0-2), but not significant (*P* > 0.05).The total drain output was more among IV group (average 350 mL) as compared to that of topical group (average 260 mL; *P* > 0.05)

Table 2: Blood loss

	Topical group(N=46)	Intravenous group (N=40)	Significance (P less than 0.5)
Average decrease in haemoglobin (g/dl)	0.9(0.4-2)	1.6(0.8-2.8)	Significant(P less than 0.05)
Blood transfusion rate (percentage of patients receiving any blood transfusion)	13%(6)	17.5%(7)	Not significant (P more than 0.05
Blood units transfused /patient	0.2 units (range 0-1)	0.3 units (range 0-2)	Not significant (P more than 0.05
Average total blood loss (ml)	1,020(650-1,550)	1,205(800-1,650)	Not significant (P more than 0.05
Average drain out put (ml) at removal time	260 (150 -500)	350 (200-600)	Not significant (P more than 0.05

Postoperatively there was oozing from the wound site in 4/40 patients (10%) in the IV group and 3/46 patients (6.5%) in the topical group. The average time of stitch removal was similar in both groups (14 days, range 12-16 days). There was evidence of postoperative infection in two cases each of the IV (0.5%) and topical group (0.43%) {table 3}

Table 3: Complications

	Topical group (N=6)	IV group(N=6)	Significance (P less than 0.05)
Oozing from wound site	3(6.5%)	4(10%)	Not significant (P more than 0.05)
Average time of stich Removal	14(12-16)	14(12-16)	Not significant (P more than 0.05)
Post operative infection	2(0.43%)	2(0.5%)	Not significant (P more than 0.05)
Post op ROM at 6 months post op	112 (90-130)	110(90-130)	Not significant (P more than 0.05)
WOMAC scores 6 months post op	89(79-96)	88(80-95)	Not significant (P more than 0.05)
Number of patients with DVT	2(0.43%)	2(0.5%)	Not significant (P more than 0.05)
Number of patients with pulmonary thromboembolism	0	0	Not significant (P more than 0.05)

No significant difference was there in postop ROM and WOMAC scores of the two groups (TABLE 3). There was also no difference in the incidence of thromboembolic findings (two cases each of DVT for topical (0.43%) and IV group (0.5%) and no cases of symptomatic pulmonary thromobembolism in either of the groups).

Discussion

In the last decade or so there have been many numerous trials, studies, and meta-analysis to evaluate TXA as a new means of chemo-hemostasis. [1],[2],[3],[4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14].

The main advantages of this drug are easy availability, repeatability, economical, less complications, and easy administration of the drug. [5],[7],[8] The drug has been routinely used in our set up since many years now in the usual IV mode of administration. The use of this drug is not limited to arthroplasty or replacement surgeries, but in other traumatic conditions requiring quick hemostasis .[2],[5] The topical usage of this drug is seen in many dental, cardiac, and spinal surgeries. [21],[22],[23] Wong *et al*., first trialled on intraarticular administration of this drug and reported significant blood loss prevention . [2] But this trial did not have any inbuilt controls of IV TXA. Plasma level of this drug was evaluated after topical administration and showed significantly less (70% less) levels as compared to an equivalent IV dose. The authors have concluded that there might be some form of action, minimal due to systemic absorption of the drug. But these levels were checked more than 1 hour after the application of this drug. It is proved

that the action of this drug TXA is actually only in the first few hours after surgery as it acts as a fibrinolytic inhibitor. The 1 hour after release of tourniquet is the crucial time when this drug reaches its maximal hemostasis .[9],[14] In our study we open the suction drain tube after an hour of application and still have managed excellent results, still proving that this 1 hour is the most important time for action of this drug"(TXA).The maximum plasma concentration is achieved in 30 min after intramuscular administration. [24],[25] Also the half-life of the drug is less than 3 hour, [2],[3],[10] and therefore there is a acceleratteddecrease in plasma levels of this drug. Therefore, the plasma values that Wong *et al*., have measured might be misleading. Ishida *et al*., [6] Sa-Ngasoongsong *et al*., [7] and Roy *et al*., [8] have conducted similar studies recently, but both of them have used normal saline placebos. To clearly prove the topical efficacy of this drug it has to be compared with an IV control group and this is what we have done in our study . Our study have shown better results for the intraarticular administration group where it clearly proves that the drug has a good local action in curtailing postoperative blood loss.

In comparison with Wong *et al*., [2] our study had some differences in methodology and results obtained . Firstly, as we have mentioned before, we are comparing intraarticular administration with IV administration and not placebos. Secondly, our method or type of administration was also a little different. They have applied the drug topically on the surface of the exposed wound before closure, without any drain (suction tube) and then tourniquet was released only after pressure bandaging but we have instead practiced deflation of tourniquet at the end of cementationprocess, careful hemostasis, and wound closure following drug delivery by injection. We believe this is very importantly identification of any inadvertent large vessel leak. Routinely suction drain is used by us, but it was opened after a period of 60 min which we felt were sufficient for the topical action of the drug. Similar type of practice has been done by others like Sa-Ngasoongsong *et al*. [7] Less amount of dosage for intraarticular injection (1 g)was used as compared to their intraarticular administration (1.5 g). So that both these studies calculated the blood loss by means of difference in pre- and postop haemoglobin value, tourniquet timing should not be a confounding factor. Slightly better results were achieved with this technique than Wong *et al*., in terms of total blood loss with intraarticular administration of 1.5 g TXA (1,020 mL as compared to 1,295 mL). In another condition where 3 g instead of 1.5 g of TXA were used by them, they have got slightly lesser blood loss (1,208 mL), but still more than what we got in our study. By the usage of 3 g, they have managed to reduce blood transfusion amount to zero. In study done by us the blood transfusion rate was similar to their 1.5 g (13%).

On correlating with other trials on IV TXA for TKAs, variable results in terms of blood loss control was obtained. We see significant reduction in decrease in haemoglobin level. Blood transfusion rates and drain outputs were also less but not much significant. In our study the total blood loss for the intraarticular administration group or patients is lower than most trials (1,020 as compared to 1,301 for Alvarez *et al*., [5] and 1,225 for Molloy *et al*., [18]). The drain output was also less than most studies conducted (260 mL as compared to 385 mL of Good *et al*., [17] and 478 for Zhang *et al*. [19]). On the other hand, blood loss and drain output for the IV group were equivocal with these studies. [5] Blood transfusion rate is difficult to compare because of the nonstandard criteria used for transfusion. When compared to studies using the same criteria as we used, the requirement for the topical group (13%) was comparable to other studies (12% for Alvarez *et al*., [5]and 13% for Veien *et al*., [16]) and slightly higher for the IV group (17.5%). The reason might be because as we have chosen a lower value of hemoglobin level(10 mg/dL for females and 11 mg/dL for males) as exclusion criteria in our study.

The rate of complication and postop functions were similar for both groups in our study. They are also comparable to all other studies of TXA, which have again show a same rate to non-TXA studies. [3],[5],[13],[14] Any increased risk of thromboembolic phenomenon since this is the greatest theoretical risk of this drug. But like most other studies, [3],[9],[14] our study also confirmed that the TXA, even topically has no risks. Although our study showed similar results for both groups it is seems but if any increased risks of thromboembolism did exist with this drug it would be lesser with intraarticular administration than IV administration. [2]

Finally we haveconcluded that intraarticular usage of TXA is as effective if not better than its IV use in controlling postoperative blood loss in TKA. Since this drug has low systemic absorption, this route forms a good alternative to the traditional IV route. More studies would be needed to substantiate the use of this route of TXA administration.

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