

## Topical usage of Tranexamic Acid: Comparative Analysis in Patients with Bilateral Total Knee Replacement

Praveen Sarada<sup>1\*</sup> and Sattar Alshryda<sup>2</sup>

<sup>1</sup>Department of Trauma and Orthopaedics, MRI, Manchester, UK

<sup>2</sup>Department of Orthopaedics, RMCH, Manchester, UK

\*Corresponding Author: Praveen Sarada, Department of Trauma and Orthopaedics, MRI, Manchester, UK.

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### Abstract

**Aim:** Topical Tranexamic acid (TXA) application provides maximum concentration of TXA at the bleeding site and avoids potential systemic effects. A number of blinded randomized control trials (RCT) have been published proving its safety and effectiveness. We hypothesised that in a person undergoing total knee replacement, if TXA was used topically on one side, it would reduce blood loss compared to the other.

**Methods:** A cohort of twenty-eight patients who were part of a larger randomized control trial was identified. Each patient had sequential bilateral TKR; one side received placebo in the form of normal saline, while tranexamic acid had been used on the other side. The primary outcome was blood transfusion rate. Comparing the blood loss separately in two knees of the same patient has the added advantage of reducing any bias that may be present due to inherent physiological differences in individuals.

**Results:** 6 (21.5%) patients needed blood transfusion following TKR on the placebo side while none needed on the side where tranexamic acid was used. Average postoperative hemoglobin and haematocrit drop was 3.2 and 0.09 respectively on the placebo side. This compared to 1.8 and 0.05 respectively on the test (TXA) side. Average drain output on the placebo side was 468.64 ml compared to 261.6 ml on the test side.

**Conclusion:** In the same patient undergoing TKR on both side, topical application of Tranexamic acid resulted in significant reduction of drain output, Hb drop and blood transfusion rates when compared to the knee where it wasn't used.

**Keywords:** Tranexamic Acid; Blood Loss; Blood Transfusion; Bilateral TKR

### Abbreviations

TXA: Tranexamic Acid; TRALI: Transfusion-Related Acute Lung Injury; TKR: Total Knee Replacement; RCT: Randomised Control Trial; LOS: Length of Stay

### Introduction

Total knee replacement (TKR) is a common operation in Orthopaedic surgery, with nearly 82,000 primary knees reported in England and Wales in 2015 [1]. Contemporary operative techniques have considerably reduced the need for blood transfusion after TKR to less than 10%, although transfusion rates still vary widely across England, from 0 - 39% [2,3]. Allogeneic transfusion poses small risks of haemolysis, infection, immunosuppression, transfusion-related acute lung injury (TRALI) and even death [4-6].

Tranexamic acid (TXA) is a synthetic antifibrinolytic agent that has been used successfully to stop bleeding. Numerous studies have confirmed the efficacy of TXA in reducing blood loss and transfusion requirements in TKR when used intravenously [7,8] but there have been sporadic reports of thromboembolic complications following intravenous administration of tranexamic acid [9,10].

We investigated the effect of topical TXA on blood loss and transfusion rate after TKR in a randomized controlled trial (RCT) [11] that proved topical TXA to be an effective and safe method to reduce blood loss and blood transfusion without increasing adverse effects. There was recognition that while randomization and masking can minimize the bias due to various external factors, they do not completely eliminate natural physiological variations inherent to individual participants. Hence, we decided to look at a cohort of patients who underwent knee replacement on both sides, in which one side was randomized for TXA and the other side was not. We hypothesized that the knee where TXA was used, would have reduced blood loss and transfusion requirements, and expected that such a comparison would eliminate any intrinsic metabolic bias from the outcomes.

### Methods

#### Study design and patients

In a study conducted at the University Hospital of North Tees and Hartlepool, 157 patients were randomised for a trial comparing the effect of tranexamic acid against placebo following topical application, around 78 in each cohort [11]. The database of the aforementioned trial was revisited in 2013 to identify patients with bilateral knee replacement in the tranexamic acid cohort. Twenty-eight patients (56 TKR) were identified. The knee that had been randomized for TXA was regarded as the active treatment while the other knee only had saline (routinely used for washout before closure) and served as control.

The primary outcome was the rate of blood transfusion during the index episode. Secondary outcome measures were blood loss, the volume of blood transfused; haemoglobin and haematocrit changes on the second postoperative day, length of stay and knee joint range of motion.

The operative technique for TKR, drain protocol, measures for DVT prophylaxis and blood transfusion protocol remained standard during the whole period when the procedures were undertaken. Patients in this cohort underwent exactly the same operation, by the same group of surgeons, in the same hospital. This study is being presented as a matched cohort study comparing the results in both knees when the only intervention variable was topical application of tranexamic acid, thus minimizing the bias resulting from inherent physiological differences.

#### Drug Delivery

The knee was washed out with saline at the end of the operation, and 1g TXA/50 ml saline was sprayed into the wound before closing the capsule as per the protocol. The drain was inserted and remained clamped for 30 min. The wound was closed in layers, dressed as usual and tourniquet released. The control group was given normal saline as placebo. The drain protocol remained the same.

#### Blood transfusion protocol

The routine transfusion protocol followed is based on the recommendation of British Orthopaedic Association (BOA) [12] and The British Committee for Standards in Haematology [13], i.e. blood transfusion: is not indicated when haemoglobin concentration is above 10 g/dl; is indicated when haemoglobin concentration is < 7 g/dl; is indicated when haemoglobin is between 7 and 10 g/dl and the patient shows symptoms of anaemia like pallor, tachycardia and easy fatigability interfering with postoperative rehabilitation.

#### Thromboembolism prophylaxis protocol

Departmental policy before and during the trial period dictated that all the patients receive mechanical thromboprophylaxis in the form of calf pump; patients with BMI > 30 additionally received chemical thromboprophylaxis with low molecular weight heparin.

**Analysis**

Continuous outcomes (such as blood loss, volume transfused, haemoglobin and Haematocrit drop) were analysed by two sample t-test. Categorical outcomes such as blood transfusion rate and complications were analysed by Fisher exact test. All tests were considered statistically significant at the 5% (p < 0.05) level.

**Results**

Fifty-six knees (28 patients; 13 females and 15 males) were included in the study. They had similar baseline characteristics (Table 1). No patient was lost to follow up. The average age at the time of surgery was 62.7 years for the placebo side and 62.1 years for the TXA side. The median difference in intervention between placebo knee and test knee was 2 years. A review of the records revealed that the patients had similar co morbidities and medications during operation for both sides and their ASA grading remained the same. As such they could be considered physiologically comparable at the time of both operations.

Variables	Control	TXA
Number	28	28
Age (y)	62.77 (SD 18.86)	62.15 (SD 9.33)
BMI (kg/M <sup>2</sup> )	32.05 (SD 6.64)	32.07 (SD 6.75)
Prescribed antiplatelets (%)	8 (28.5%)	8 (28.51%)
Prescribed NSAID (%)	9 (32%)	9 (32%)
Preoperative HB (g/dl)	13.9 (SD 1.2)	13.3 (SD 1.2)
Preoperative Hct	0.405 (SD 0.035)	0.391 (SD 0.036)
Preoperative ROM (°)	92.5 (SD 6.7)	94.5 (SD 16.38)
DVT prophylaxis (LMWH) (%)	17 (61%)	14 (50%)
Tourniquet time (min).	76 (SD 20.2)	74 (SD 15.2)
Anaesthesia (spinal)	25 (89%)	25 (89%)

**Table 1:** Baseline characteristics of the study population.

**Blood transfusion**

Six participants (21.5%) on the placebo side required blood transfusion but none in the TXA side; a statistically significant reduction in the use of transfusion (p = 0.023), (Table 2). The six transfused participants received between 2 and 3 units, 14 units of blood in total.

	Placebo	TXA	Δ (95% CI), p
<b>Primary endpoint</b>			
Transfusion	6/26 (21.5%)	0/26 (0%)	21.5% 7.5% to 25.4%; p=0.023
<b>Secondary endpoints</b>			
Drain Blood Loss, ml	468.64 (SD 401), N=22	261.6 (SD 233), N = 25	207.04 (17 to 397), p = 0.033
Postop Hb, g/dl	10.63 (SD 1.37), N = 24	11.56 (SD 1.21), N = 26	-0.93 (-1.67 to -0.196), p = 0.014
Postop Hct	0.31 (SD 0.04), N = 24	0.34 (SD 0.03), N = 26	-0.031 (-0.052 to -0.009), p = 0.005
Length of Stay, days	6.4 (SD 2.4), N = 25	5.4 (SD 3.5), N = 25	0.96 (-0.742 to 2.662, p = 0.263

**Table 2:** Primary and secondary outcomes.

**Blood loss**

The mean drain blood was 468.64 ml in the placebo side and 261.6 ml in the TXA side. The mean difference was 207.04 ml (95% CI 17 to 397), p = 0.033 ml.

**Postoperative haemoglobin and haemocrit**

Haemoglobin (Hb) and haemocrit (Hct) were tested on postoperative day 2 unless there was a clinical need to do these earlier. The drop of postoperative Hb in TXA group was 0.93g (p = 0.014) less in the TXA group when compared to placebo. Similarly, a statistically significant reduction of drop in postoperative Hct (-0.031, 95% CI -0.052 to -0.009, p = 0.005) was observed in the TXA group when compared to placebo.

**Adverse events (Table 3)**

Complications	Placebo	TXA	p
Deep Venous Thrombosis	0	1	
Pulmonary Embolism	0	0	
CVA / TIA	0	0	
Chest infection	0	0	
Anterior knee pain	2	0	
Periprosthetic fracture	0	1*	
Superficial infection	1	0	
Deep infection	0	1*	
Revision	3	2*	

**Table 3:** Complications during the trial.

*\*This patient sustained patella fracture after three months, for which she had surgical intervention. This was complicated by deep infection and needed two stage revision.*

In the TXA cohort, one patient developed deep vein thrombosis and another needed joint arthrolysis and patellar resurfacing. One patient in the control group had infection and another one knee needed manipulation under anaesthesia for postoperative stiffness. None of the adverse effects were statistically significant.

**Discussion**

Topical application of TXA appears to be an effective and safe way to reduce blood loss and blood transfusion without extra adverse effects. As per a Cochrane review in 2009 [14]. TXA seems to be at least as potent as aprotinin, but potentially safer and with a better cost-effectiveness profile [15]. De Bonis and colleagues [16] showed that there was no detectable blood level of TXA after topical application.

The results of an RCT [11] confirmed the hypothesis that topical application of Tranexamic acid can be safely used to reduce blood loss and the need for allogenic blood transfusion. In addition, this trial demonstrated that there was no difference in functional outcomes following such an intervention.

However, even the most rigorous methodology of an RCT cannot prevent inherent bias as a result of physiological differences among individuals. This confounding factor can be best minimized by comparing the result of TKR in both knees of the same individual, where the only difference between the two sides has been intervention in form of topical TXA as part of the RCT. We therefore looked at the test

cohort from the original RCT to filter patients who had undergone bilateral TKR but no Tranexamic acid was used on the other side. This resulted in a cohort of 28 patients (56 knees). Post hoc analysis of this study revealed that to drop transfusion rate from 21.5% to 0 would only need 27 patients (54 knees) to achieve 80% power.

The Cochrane collaboration [17] suggests using 'body-part analysis' to distinguish between two different types of interventions involving similar parts of the body. They advocate use of paired analyses for such groups. We have used paired T tests and independent samples test to analyze our results using SPSS 19 software.

The results of this study confirm that none of the patients needed blood transfusion in the knee where tranexamic acid had been used, while 6 (21.5%) needed it on the opposite knee where no such intervention had been done. In addition, there was statistically significant reduction in drain blood loss, hemoglobin drop as well as haematocrit drop, which confirms that it leads to reduction of the "hidden blood loss" as well. The primary and secondary end points have been summarized in table 3. These results are in line with recent published RCTs involving topical usage of TXA [11,18]. However, this study presents a unique perspective to the results because such a comparison of bilateral TKAs has not been published before.

The length of stay (LOS) reduced by around one day but did not reach statistically significant levels. However, the results were skewed by an outlier in TXA group who stayed for 20 days due to chest infection. When calculations were repeated after excluding this patient, LOS was also found to be significantly reduced ( $p = 0.044$ ). The results therefore suggest that adopting routine use of topical TXA can also potentially result in significant cash savings.

We have not included functional scoring for comparing results because at the time of scoring the first TKR, the scores may be lowered due to pain from the other arthritic knee. We did not detect any significant difference in the range of movement of both knees, and in general the function remained satisfactory unless patients had any documented complications as above.

A weakness of this study is that part of the placebo group (12 knees) had retrospective review of prospectively collected data and therefore not as robust as a level I evidence, but the data relates to biochemical values and as such was no inferior than that collected during the trial. It is also theoretically possible that patient's physiologic status may have changed between the two operations, but we have looked at various parameters to conclude such variation was practically nonexistent. The median time interval between the two sides was only two years. Moreover, a review of the notes confirmed there was no change in their medication, ASA status or significant BMI variation between the two operations (Table 1). It is therefore safe to assume that their physiological status had not significantly altered in the interim.

### Conclusion

In conclusion, this study proves that blood loss after TKR was significantly less in the knee where TXA had been used compared to the other side. We can therefore confirm excellent result from topical usage of tranexamic acid in TKA after minimizing physiological bias.

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