

Preventing the preventable: role of transamine in total knee arthroplasty

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Abstract

Objectives: To assess the efficacy and safety of perioperative intravenous Tranexamic Acid in reducing blood loss and transfusion requirements in patients undergoing Total Knee Arthroplasty.

Methods: The prospective double-blind randomised control trial was conducted from March to July 2014 at the Combined Military Hospital, Rawalpindi, and comprised patients below 85 years of age undergoing unilateral or bilateral cemented Total Knee Arthroplasty. The patients were divided into control or Transamine groups. Two doses of 15mg/kg of Transamine were given to the latter group. All patients were operated under spinal or combined spinal-epidural anaesthesia using pneumatic tourniquet and similar cemented implant. Primary outcome was postoperative blood loss in drains. Secondary outcomes were the number of blood units transfused, change in haemoglobin level and adverse events.

Results: Of the 62 patients on the study, there were 34(55%) patients in the Transamine group with a mean age of 64±8.4 years, and 28(45%) in the control group with a mean age of 60.8±10.3. The two groups were matched for demographic and blood indices. Mean blood loss via intra-articular drain in the control group was 619±243ml per knee, and 402±169ml per knee in the Transamine group. Blood transfusions were required by 14(50%) patients in the control group and 6(17.6%) in the Transamine group.

Conclusion: Perioperative intravenous transamine significantly reduced blood loss as well as blood transfusion requirements.

Keywords: TKA, Tranexamic acid, Blood Transfusion. (JPMA 64: S-44 (Suppl. 2); 2014)

Introduction

Blood loss in patients undergoing Total Knee Arthroplasty (TKA) is a serious concern. Estimated blood loss reported for single TKA varies between 600ml to 1800ml.^{1,2} In elderly patients undergoing simultaneous bilateral knee replacements, having low physiological reserves, the loss sometimes leads to catastrophic results. It is reported that the tourniquet used in TKA is associated with increase in localised fibrinolysis, leading to two events. Firstly, it may aggravate postoperative haemorrhage and, secondly, it decreases the risk of venous thromboembolism (VTE).¹

Allogenic blood transfusions are required in 50-60% of such cases to treat acute blood loss and to prevent potential cardiovascular risks.³ Allogenic blood transfusion itself is associated with risks of immunological reactions, immunosuppression and infection transmission.^{3,4}

A variety of blood-conserving techniques have been developed to reduce blood loss and avoid allogenic blood transfusions like preoperative blood donation,

perioperative red cell salvage, hypotensive anaesthesia, use of fibrin glue and antifibrinolytic agents like Tranexamic Acid [TXA], Aprotin, E-Aminocaproic Acid [EACA]. Amongst all of the them, TXA has gained popularity as it is cost-effective, safer and much more potent than other antifibrinolytic agents.⁴

TXA inhibits fibrinolysis by competitively blocking the lysine-binding sites of plasminogen. It prevents clot breakdown and re-bleed. It has been used successfully to reduce blood loss in cardiac surgery, liver surgery, traumatic haemorrhage and gynaecology.⁵

There is still a lack of consensus in the protocol of administration of TXA as well as the dose of TXA.^{5,6} Most studies used bolus concentrations of 10mg/kg, 15mg/kg and 20mg/kg. Although there is a direct relationship of the amount of TXA given to reduction in perioperative blood loss⁶ but a continuous administration of a larger dose of TXA [>20mg/kg] may cause thromboembolism.⁴

The efficacy of TXA administered intravenously (IV) in preventing blood loss in TKA has been reported in numerous studies, but only one retrospective study so far has been documented in Pakistan.¹ This is the first reported prospective randomised control trial on TXA efficacy in preventing blood loss in TKA from Pakistan.

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Patients and Method

The prospective double-blind randomised control trial was conducted from March to July 2014 at the Combined Military Hospital, Rawalpindi, and comprised patients below 85 years of age undergoing unilateral or bilateral cemented TKA. Patients with history of thromboembolic disease, myocardial infarction (MI), bleeding disorder, previous surgery on the same knee, known allergy to TXA, receiving anticoagulant drug treatment and age more than 85 were excluded.

After obtaining approval from the institutional ethics committee, informed consent was obtained from all patients.

The patients were divided into control (C) or TXA (T) groups by selecting a sealed envelope randomly by an anaesthetist 15min before the start of the surgery. In the C group, TXA was not given, while in the T group a first dose of 15mg/kg weight of TXA was slowly infused 15-20 minutes before tourniquet release. A second identical dose was administered after 3 hours in the recovery room.

Preoperative data, including age at the time of the operation, gender, body mass index (BMI), preoperative haemoglobin level, prothrombin time [PT], activated partial thromboplastin time [APTT] and platelet count were obtained. The demographic and blood indices were similar in both the groups.

All patients were operated under spinal or combined spinal-epidural anaesthesia using pneumatic tourniquet. Similar cemented implants were used in both groups. [DePuy PFC Sigma PS/CR, DePuy RPF or Zimmer Nex Gen LPS Flex with patellar component]. In each knee, one intraarticular drain (14-gauge) was placed in the lateral gutter and was connected to a high-vacuum drain bottle. The drains were placed for 24-48 hours depending on the total outflow in the preceding 24 hours.

The total volume of drained blood upto 48 hours postoperatively was recorded in the wards by the attending doctor blinded to the study groups. Haemoglobin and haematocrit were checked immediately postoperatively, 24 hour and 48 hours after the surgery.

The need for blood transfusions was considered when haemoglobin was below 8.5gm/dl in healthy patients or between 8.5 and 10gm/dl in patients with signs and symptoms of anaemia. In patients with cardiovascular diseases, the transfusion threshold was adjusted to haemoglobin level of 10gm/dl.⁴ However, during surgery, especially in patients undergoing bilateral TKA, blood transfusions were made on the recommendation of

anaesthetist incharge, based on patient's clinical condition. Blood transfusions were recorded as the number of units of packed erythrocytes given in the perioperative period.

In the immediate postoperative period, patients were advised passive ankle pumps followed by active ankle pumps soon after they regained motor functions in lower limbs. Patients were made to sit up with legs hanging down the bedside the next morning and were encouraged to stand up on second post-operative day. On the second post-op day, the patients were allowed walking with support. As soon as a patient was able to walk up to the washroom with support, the urinary catheter was removed and the patient was ready for discharge on about 3rd to 4th postoperative day.

Cardiovascular, thromboembolic and other complications (e.g. wound complications) were noted during the hospital stay, at two weeks and six weeks follow-up. The presence of deep venous thrombosis [DVT] was evaluated by inspecting for thigh and calf swelling or oedema >3cm compared with the contralateral leg along with calf tenderness.³ If DVT was suspected, Doppler ultrasound of the leg was performed, while computed tomography pulmonary angiography (CTPA) was performed if there was suspicion of pulmonary embolism (PE).

Differences in the mean age, preoperative and postoperative haemoglobin volume of drained blood, decrease in haemoglobin 24 and 48 hours postoperatively and the mean number of transfused units between the two groups were determined using Student's t test. The number of patients requiring blood transfusion and those not requiring blood transfusions in the groups were analysed using the chi square test.

Results

Of the 62 patients in the study, there were 34(55%) patients in the Transamine group (T) with a mean age of 64 ± 8.4 years, and 28(45%) in the Control group (C) with a mean age of 60.8 ± 10.3 . Within the C group, there were 18(64.3%) females and 10(35.7%) males, with age ranging between 48 and 79 years. In the T group, there were 22(64.7%) females and 12(35.3%) males with age ranging from 45 to 78 years. The two groups were matched for demographic and blood indices (Table-1). Overall TKAs in the 62 patients were 96; 43(45%) in the C group and 53(55%) in the T group. In the C group, 15(53.5%) patients had bilateral TKA and 13(46.5%) had single-knee TKA. In the T group, 19(56%) had bilateral procedure and 15(44%) had single-knee procedure. In the C group, the right knee was operated upon in 25(58%) cases and the left in 18(42%). In the T group, there were 31(58.5%) right

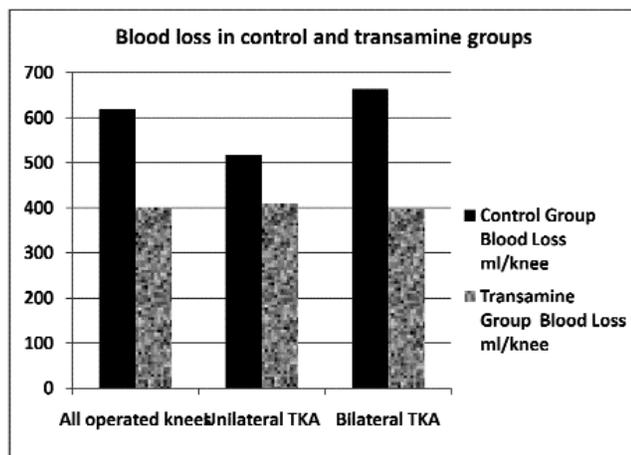
Table-1: Demographic details.

| Group | Number | Females | Males | Average Age years | Average Weight kg | Average Height m | Average BMI |
|------------------|--------|---------|-------|-------------------|-------------------|------------------|-------------|
| Control Group | 28 | 18 | 10 | 64 ± 8.4 | 85.8 ± 18.3 | 1.64 ± 0.1 | 33 ± 6.7 |
| Transamine Group | 34 | 22 | 12 | 60.8 ± 10.3 | 78.4 ± 13.9 | 1.6 ± 0.1 | 29.8 ± 5.6 |

BMI: Body Mass Index.

Table-2: Comparison of blood loss via drain in control and transamine groups.

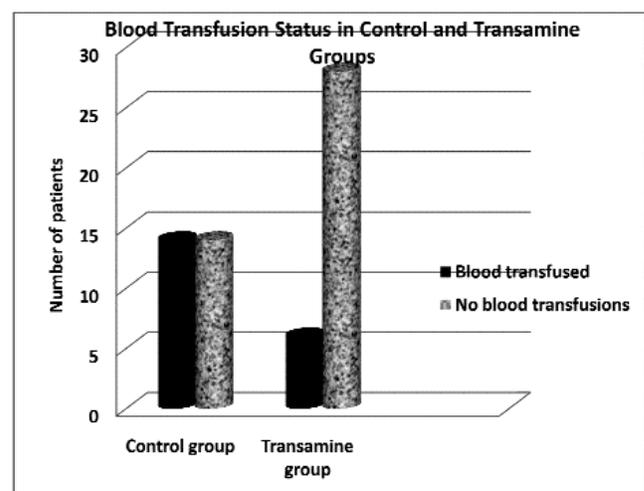
| | Control Group Blood Loss ml/knee | Transamine Group Blood Loss ml/knee | P-value |
|---|----------------------------------|-------------------------------------|---------|
| All operated knees | 619 ± 243 | 402 ± 169 | 1.4E-06 |
| Single operated knees | 518 ± 230 | 409 ± 187 | 0.18 |
| Bilateral operated knees | 663 ± 239 | 398 ± 164 | 9.6E-07 |
| First operated knee in bilateral cases | 708 ± 239 | 434 ± 185 | 0.0007 |
| Second operated knee in bilateral cases | 617 ± 237 | 363 ± 164 | 0.0004 |

**Figure-1:** Comparison of blood loss in control and transamine groups.

knees and 22(41.5%) left knees.

Mean blood loss via intra-articular drain in the C group was 619±243ml per knee, and 402±169ml per knee in the T group (Table-2; Figure-1). In unilateral TKA, the loss in C group was 518±230ml compared to 409±187ml in the T group. Bilateral TKA cases in T group showed loss of 398±164ml against a loss of 663±239ml in C group.

Blood transfusions were required by 14(50%) patients in the C group and 6(17.6%) in the T group (Figure-2). In the C group, a total of 17 pints were transfused, averaging 0.61±0.69 pints per patient. In the T group mean 0.18±0.39 pints were required. The difference between the number of patients requiring blood transfusions and those not requiring blood transfusions in control group were statistically significant (p=0.006). Further, 9(60%) patients undergoing bilateral TKA in the C group required blood

**Figure-2:** Blood transfusion status in control and transamine groups.

transfusions as against 5(26.3%) in the T group (p<0.05).

The mean amount of blood transfused was 0.79±0.70 in bilateral TKAs in C group and 0.28±0.46 in T group. In unilateral TKAs, 3(23%) of C group patients and 1(6.7%) T group patient received blood transfusions (p>0.05). Mean amount of blood transfused in unilateral TKA was 0.31±0.63 in C group and 0.07±0.26 in T group.

Preoperative haemoglobin levels were quite similar in the two groups; 12.7±1.5 and 12.8±1.4 g/dl. The average haemoglobin declined to 10.6±1.4 g/dl postoperatively in the C patients, and to 11.1±1.5g/dl in the T group, registering an average fall of 2.02±1.19g/dl and 1.67±1.0g/dl respectively. Within each group (C and T) and subgroups (bilateral and unilateral TKAs), the difference between pre and postoperative haemoglobin

levels was significant ($p < 0.05$ each).

When comparing the two groups, the use of TXA was not associated with any additional adverse effect like DVT or wound complications.

Discussion

Our study suggests TXA reduces total blood loss and transfusion requirements after TKA.

It also shows that TXA has a more profound effect on reduction in blood loss and thus reduction in number of transfusions required in patients undergoing bilateral TKA than unilateral TKA. One reason for this may be that the effectiveness of TXA in reducing blood loss is more appreciable when the blood loss in the control group is 1L or more, as stated in some studies.^{7,8}

Although there is a long debate about the number of doses and the time of administration of doses, but the more recent studies support that two-drug regimen is better than the single-dose regimen.^{2,9}

A study compared the effects of five different dose regimens; two single-dose (intra-operative intravenous [IO-IV] and intra articular [IA]), two double-dose (preoperative, intraoperative [PO-IO] and intraoperative, postoperative [IO-PO]) and a three-dose [preoperative, intraoperative, postoperative [PO-IO-PO]] regimen and found the three-dose regimen to be the most effective.² Emphasising upon the importance of preoperative dose of TXA, the study noted, "Fibrinolysis activation begins with surgical trauma and is further enhanced by tourniquet inflation. Giving TXA preoperatively 15 minutes before tourniquet inflation, so that it reaches its peak plasma concentration in the surgically-treated limb before tourniquet inflation, would deactivate fibrinolysis as soon as it starts. Fibrinolysis, being a cascade reaction, is best inhibited in the initial stages, and this is best achieved with a preoperative dose." Another study¹⁰ came to the same conclusion regarding the preoperative dose.

In our series of bilateral TKA patients, if we consider that the IO dose given for first knee has a preoperative effect on the second knee [as the second knee surgery started 20 to 30 minutes after the IO dose of TXA], there should be less blood loss in the second knee. In our experience in patients undergoing simultaneous bilateral knee replacement, the blood loss from the second knee was slightly [90 ml] less than from the first knee but the difference was about the same present in the two knees of the control group [70 ml]. So our study shows that IO dose given 15 minutes before deflation of tourniquet is equally as effective as preoperative dose of TXA.

We used a -drug regimen [IO-PO] and found it very effective as the postoperative blood loss in drains decreased from 619cc in the C group to 402cc in the T group and the rate of transfusion from a rate of 50% in the C group to 17% in the T group. Our results are in consistence with recent studies.^{9,11,12}

Our results as well as others^{1,2} support that 2 doses of IV TXA at 15mg/kg do not enhance the chances of any untoward effect e.g. DVT. For a precise incidence evaluation of postoperative DVT, patient should be followed for at least 3 months with modalities like Doppler ultrasound.

Blood transfusion is associated with high frequency of viraemia, in most of the study populations from third world countries, with values ranging from 16 percent in Pakistan to 83 percent in Gambia.¹³ Another large-scale study in Pakistan has shown that the screening coverage for blood products on the average has been 77.4% for human immunodeficiency virus (HIV) and 86.8% for Hepatitis B Virus (HBV). Although the prevalence of HIV is 0.001% and of HBV is 2.2%, the probability of receiving an infective unit per 10000 donations is 0.02 for HIV and 29.7 for HBV.¹⁴ Perioperative allogeneic blood transfusion, due to its immunodilution effect, is also associated with a higher rate of acute infection leading to re-operations.¹⁵

Coming to the cost effectiveness of TXA over blood products, one unit of red cells costs about 120 pounds in England and 19 pounds in Pakistan.¹ The regimen of TXA that was administered in our study population costs about 3 pounds. Another study using the same TXA dose regimen revealed saving an average of 240 Euros per unilateral TKA procedure; not considering the indirect savings related to allogeneic transfusion risks and derived expenditure.¹¹ A systemic review revealed that analyses of cost effectiveness of five studies were all in favour of using TXA over other blood products.⁶ By reducing the requirement of blood transfusions, we can decrease burden on healthcare systems and on individuals paying for their own health.

Conclusion

TXA significantly reduced postoperative blood loss and transfusion requirements after primary TKA without important additional adverse effects. Reduction in transfusion requirements not only decreases its associated side effects, but also decreases economic burden on healthcare systems and on individuals paying for their own health.

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