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Original Research Article

Impact of tranexamic acid on coagulation parameters in patients undergoing total knee replacement surgeries under tourniquet: an observational study

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ABSTRACT

Background: A growing body of evidence has shown Tranexamic Acid (TXA) is effective in decreasing perioperative blood loss and transfusion requirements in both primary and revision joint arthroplasty. TXA is a synthetic drug which limits blood loss through inhibition of fibrinolysis and clot degradation. It helps reduce requirement of colloids and crystalloids and hence provides better haemodynamic stability. The aim of this study was to detect the effect of tranexamic acid on coagulation parameters and effect on bleeding in knee replacement surgeries performed under tourniquet.
Methods: Patients undergone surgeries of Total Knee Replacement (TKR) performed under tourniquet were included in the study. A single dosage of 20 mg/kg per body weight of tranexamic acid was administered after application of a tourniquet. Three times blood sample was collected, and coagulation parameters were recorded and compared. The first sample was collected at the time of TXA injection and application of a tourniquet, second after 4 hours and third after 24 hours post TXA injection. Coagulation parameters noted were analyzed using Statistical analysis by SPSS software. All parameters were compared in relation to baseline i.e. at the time of TXA injection.
Results: On comparison of demographic profile, morbidity, sofa score and hemodynamic parameters there was the insignificant difference ($P > 0.05$). Repeated measures of ANOVA at 95% Confidential Interval P value was 0.000 which is less than the significant level that is 0.05 so that value of Platelet Function (PF), Activated Coagulation Time (ACT) and Clot Rate (CR) at 0 hrs, 04 hrs and 24 hrs was statistically significant. Correlation between blood loss and difference of the value of ACT at 0 hrs and 04 hrs is a small negative correlation but statistically nonsignificant (P value is 0.359).
Conclusions: After TXA administration there is a change in coagulation parameters like an Activated Coagulation Time (ACT), Platelet Function (PF), and Clot Rate (CR) measured at three intervals, hence it can be a guide to detect early derangement in the coagulation profile in a patient undergoing knee replace surgery. TXA correlation between blood loss with changes in parameters of coagulation i.e. ACT, PF and CR were noted but not significant.

Keywords: Blood loss, Cement, Knee replacement, Platelets, Thrombosis, Tourniquet

INTRODUCTION

Perioperative blood loss is a significant concern for patients undergoing total joint arthroplasty. A number of strategies are employed in order to minimize blood loss in orthopedic surgery. It has been observed that the use of tourniquets and meticulous surgical technique like

ligating or cauterizing vessels provides relatively avascular operative field.[1]

Strategies to avoid allogenic blood transfusion include the use of autologous blood by predonation, acute normovolemic hemodilution (ANH) and cell salvage. The main drawback is that they are cumbersome, require specialized equipment and trained staff. Reports of coagulation disorders have been associated with the use of Cell salvage.[2]

Pharmaceutical preparations such as erythropoietin, TXA and aprotinin were reported to be used in reducing bleeding and postoperative transfusion requirements. Antifibrinolytics such as TXA are used routinely in gynecology, trauma and orthopedic and are inexpensive. TXA is known to be effective in decreasing perioperative blood loss and transfusion requirements in both primary and revision joint arthroplasty. TXA is a synthetic drug that limits blood loss through inhibition of fibrinolysis and clot degradation. Both topical and intravenous administration of TXA in a variety of dosing regimens has been proven effective. It inhibits fibrinolysis by blocking the lysine binding sites of plasminogen to fibrin.[3,4]

Dosing schedules of TXA have been used in varied frequency, routes, and dosages by various researchers. Few have used an initial bolus of TXA followed by a 6- to 12-hour infusion or multiple intravenous boluses. In multiple boluses disadvantages is of intensive labor leading to compliance in busy operating theatre. Few studies followed only single dose and some bolus dosages at a fixed interval. Kagoma et al considered 21 studies in which the dose of TXA ranged from 10- to 20-mg initial bolus followed by either an infusion of 1 to 10 mg per kg per hour for 4 to 30 hours or fixed repeated doses of TXA every 3 hours ranging from one to four doses. Most commonly prescribed a dose of TXA was a 10-mg per kg initial bolus dose followed by a second similar dose at 3 hours. The optimal dose and dosing regimens are still not clear. We decided to adopt one dose of 20 mg per kg to be given before the onset of fibrinolysis. Although no conclusive evidence supports, an initial intravenous dose be given before beginning the procedure and at least one additional intravenous dose required postoperatively. In few study, topical TXA doses >2g appears to be more efficacious than lower doses.[5-7]

Authors omitted the second dose as TXA has a prolonged extra vascular effect, hence, repeat dose was not required. While clinical trials using TXA have shown promising results by reduction of blood loss and rate of blood transfusions but numerous concerns regarding complications of TXA are reported, amongst them few are non-fatal and few fatal like prothrombotic adverse events e.g. deep vein thrombosis, myocardial infarction, pulmonary embolism and cerebrovascular events. These concerns inhibit use for wide spread use.[8]

So far, there is a lack of clinical trials large enough to prove efficacy and the safety of TXA in a patient population planned for Total Joint Replacements (TJR) are prone to adverse reactions. This dilemma is further complicated by the fact that people in this age groups are considered at risk for thromboembolic complications as well as increased risk for ischemic adversities in the setting of increased blood loss. But patients at risk of Perioperative Myocardial Infarction would benefit by using TXA, as use of TXA will decrease blood loss hence anemia and higher blood transfusion rates which are the worse predictors of cardiovascular outcome after surgery. A relatively few adverse reactions have been reported in arthroplasty patients and no study has demonstrated conclusively, an increased risk of venous thromboembolic events in this patient population.[9,10]

In 1989 Haymen suggested that changes in viscosity of blood might help in the analysis of coagulation parameters. In 1910 Kauffman introduced his co coaguloviscometer first equipment capable of monitoring coagulation, but ultimately Kugelmass introduced the system of measuring the continuous elastogram which formed the basis of thromboelastograph (TEGt). In 1975 Von Kaulla and Ostrendoff described sonoclot analyzer, a device which measures the changing impedance to movement of the ultrasonic probe due to developing clot mass in a blood sample. Immersion of probe in blood initially causes impedance compare to air.

The primary slope R1 reflects initial fibrin formation, secondary slope R2 reflects fibrin formation and fibrin platelet interaction and Slope R3 reflects further platelet function and number of platelets. Samra et al studied the effects of aspirin on platelet function and prolongation of bleeding time. Stern et al found the clot retraction with sonoclot signature i.e. R3 decreases slightly in the patients receiving Aspirin therapy than those who are not. Although earlier studies have shown similar results, they have included patients with different diagnoses; dosages and timing of medication.[11,12]

This study was conducted with the aim to assess the impact of TXA on coagulation parameters. Amount of Fluid resuscitation and drugs required to maintain hemodynamic stability.

METHODS

All patients more than 18 years of age of both gender in ASA grade I and II, planned for elective surgery for past 6 months, underwent knee replacement surgery at tertiary care orthopaedic centre, after approval of local Hospital Ethical Research committee were included. Investigations related to treatment were ordered by orthopaedician like Complete Blood count, Coagulation profile and other relevant one. Patients were excluded from the study if they were suffering from any Bleeding Disorders or where TXA was contraindicated.

Study design required sample size of around sixty patients undergoing knee replacement surgery with tourniquet at this centre. Baseline sample was marked as first venous sample collected just after application of tourniquet and administration of stat dose of TXA of 20 mg/kg body weight.

Blood sample collected was analyzed within 3 minutes in OT. Coagulation parameters recorded at three different times. First baseline reading was taken just after administration of first dosage of TXA, tourniquet application and at time of incision. Second reading was recorded after 4 hours of administration of TXA and third reading was noted after twenty four hours of TXA administration i.e. the time to reverse the changes in coagulation parameters. All these parameters were recorded at three intervals and compared. Data collected in anaesthesia monitoring chart were analyzed. Study population profiling was carried out by analyzing different demographic and coagulation parameters. Quantitative data were presented in terms of means and standard deviation. Repeated measures of ANOVA test were applied using IBM SPSS 20 edition software. P-value <0.05 is considered statistically significant.

RESULTS

A total of 60 patients were enrolled in the study after applying inclusion and exclusion criteria. In Table 1 and Figure 1, demographic profile of study population and ASA status was shown. On comparison of demographic profile, morbidity, sofa score and hemodynamic parameters there was nil significant difference (P >0.05).

Table 1: Demographic profile of patients.

Age Group (yrs)	Gender		ASA			
	Female	Male	I	II	III	IV
50 - 60	7	3	1	10	0	0
61 - 70	15	16	3	25	0	1
71 - 80	7	9	0	16	1	0
81 - 90	0	2	0	2	0	0

In Table 2, after applying repeated measures of ANOVA at 95% Confidential Interval P value is 0.000 which is less than significant level that is 0.05, so value of (ACT) at 0 hrs, 04 hrs and 24 hrs was statistically significant.

Table 2: Impact of tranexamic acid on coagulation parameters (ACT).

Measure: Activated Clotting Time (ACT)					
Factor	Mean	Std. Error	95% Confidence Interval		P Value*
			Lower bound	Upper bound	
ACT 0	132.119	3.930	124.252	139.986	0.000
ACT 4	130.898	3.555	123.783	138.014	
ACT 24	130.068	3.496	123.069	137.067	

* Repeated Measures of ANOVA

Table 3: Impact of tranexamic acid on coagulation parameters (PF).

Measure: Platelet Function (PF)					
Factor	Mean	Std. Error	95% Confidence Interval		P Value*
			Lower bound	Upper bound	
PF 0	2.641	0.127	2.387	2.895	0.000
PF 4	2.608	0.125	2.359	2.858	
PF 24	3.247	0.595	2.056	4.438	

* Repeated Measures of ANOVA

Table 4: Impact of tranexamic acid on coagulation parameters (CR).

Measure: Clotting Rate (CR)					
Factor	Mean	Std. Error	95% Confidence Interval		P Value*
			Lower Bound	Upper Bound	
CR 0	36.144	1.466	33.210	39.079	0.000
CR 4	36.929	1.648	33.630	40.228	
CR 24	37.227	1.580	34.064	40.390	

* Repeated Measures of ANOVA

In Table 3, after applying repeated measures of ANOVA at 95% Confidential Interval P value is 0.000 which is less than significant level that is 0.05 so value of PF at 0 hrs, 04 hrs and 24 hrs was statistically significant.

Refer Table 4 after applying repeated measures of ANOVA at 95% Confidential Interval P value is 0.000 which is less than significant level that is 0.05 so that value of CR at 0 hrs, 04 hrs and 24 hrs was statistically significant.

In Table 5 correlation between blood loss and difference of value of ACT at 0 hrs and 04 hrs is small negative correlation which is not statistically significant (P value is 0.359) was shown.

Table 5: Correlation of coagulation parameters and blood loss after the use of tranexamic acid.

		Bld loss ml	Diff ACT 0 and 4
Bld loss ml	Pearson correlation	1	-0.122
	Sig. (2-tailed)		0.359
	N	59	59
Diff. ACT 0 and 4	Pearson correlation	-0.122	1
	Sig. (2-tailed)	0.359	
	N	59	59

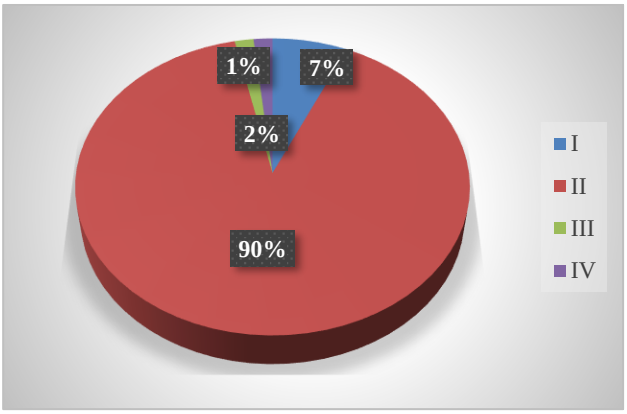

Figure 1: ASA status of patients.

DISCUSSION

Postoperative anemia following Joint replacement surgeries has been shown to increase the length of stay in hospital, delayed mobilization and is poorly tolerated by patients Ischemic Heart Disease.[1,2]

Patients with low pre-operative hemoglobin levels, undergoing bilateral hip arthroplasties, Jehovah's witness require allogenic blood products but since ethically not acceptable in these group of patients, measures to reduce blood loss are of paramount importance. The avoidance of allogenic blood transfusion is desirable in order to reduce the potential risk and cost implications.[13,14]

Reduction in blood loss and allogenic transfusion can be achieved in orthopedic surgery by using tourniquets, good surgical technique, equipment, use of autologous blood by predonation, acute normovolemic hemodilution (ANH) and cell salvage.[2,15,16]

In addition, the most significant indicator of the likelihood of postoperative transfusion is the pre-operative hemoglobin level. Around 69% requirement of allogenic transfusion was observed, if the hemoglobin is less than 13g/dl and 13% if hemoglobin is more than 15g/dl. Therefore, patients least likely to require transfusion are the most suitable for predonation.[17-19]

Pharmaceutical preparations such as erythropoietin, while effective in reducing postoperative transfusion, are very expensive. Various strategies enumerated were adopted to reduce perioperative transfusion rates. Still, search for other alternative measures to reduce blood loss and requirement of blood transfusion is still underway. Use of antifibrinolytics, specifically TXA, and Aprotonin were suggested by multiple studies but the ability of TXA to reduce blood loss and red blood cell transfusion in patients undergoing primary arthroplasties was stressed and preferred by the most.[5,20,21]

TXA is a synthetic drug that limits blood loss through inhibition of fibrinolysis and clot degradation. Both topical and intravenous administration of TXA, in a variety of dosing regimens, has proven effective. It inhibits fibrinolysis by blocking the lysine binding sites of plasminogen to fibrin. Whereas the antiprotease effects of aprotinin preserve platelet membrane receptors better than TXA. Aprotinin is an expensive drug and can induce anaphylaxis. Therefore, TXA could be a better alternative as it is inexpensive and apparently does not induce anaphylaxis but Aprotonin is good in cardiac surgery as it helps to prevent cardiopulmonary bypass induces fibrinolysis.[22-25]

The mechanism by which these drugs decrease surgical bleeding is controversial and probably various other factors play an important role like the type of total knee replacement surgery done, whether cemented or non-cemented, primary/secondary arthroplasty affects the blood loss and cemented or not cemented Joint Arthroplasty. Raut et al in their study observed that postoperative blood loss is lower in TKA after using cemented press-fit condylar prosthesis and a femoral intramedullary plug. There are reports about an increased risk for pulmonary embolism during cement injection, but they suggested that aprotinin given before cement injection had no such adverse effects. Therefore, it may be harmful to decrease the fibrinolytic capacity of the lungs during this period.[26-28]

Gomez-Barrena et al, compared topical TXA vs an intravenous application in primary total knee arthroplasty in phase III, single center, double-blind, randomized, controlled trial. They compared topical TXA (3g of TXA in 100 mL saline solution) versus two intravenous doses of TXA (15 mg/kg in 100 mL saline solution), one before tourniquet release and other 3 hours after surgery.

Plasma concentrations one hour after intravenous administration of 10mg/kg TXA have produced mean values of 18mg/L, whereas topically administered TXA resulted in lower plasma concentrations. Plasma concentration levels between 5-10mg/L are considered to be therapeutically active and hence the possibility of even topical approach has systemic effects and potentially side effects. Hence, topically administered TXA when compared to intravenously in patients undergoing total knee arthroplasty both achieved a therapeutic level of plasma concentration. More recently, a meta-analysis by Zhao-Yu et al. showed no significant differences for intra-articular use of TXA in patients undergoing total knee arthroplasty compared to placebo in regard of deep vein thrombosis or pulmonary embolism.[29-30]

It is important to understand that increased complications, like DVTs, might nullify cost vs benefits. Most important concerns for initiation of this protocol was the antifibrinolytic effect of TXA, which might lead to an increase in venous thromboembolic events. However, literature regarding this suggests TXA does not result in an increase in thromboembolic events. There is concern that TXA may promote a hypercoagulable state and cerebral, pulmonary, mesenteric, and retinal thromboses have been reported.Christie et al, have shown that cardiopulmonary. an embolism occurs during cement injection of the femoral component in THR.[28,31-33]

Although Lozano et al, reported that the use of TXA was not associated with an increase in thrombotic complications either clinically or anywhere documented radiologically. No increase in the frequency of peripheral venous thromboses was seen between the TXA group. The viscoelastic tests like TEGt and Sonoclot coagulation data didn't report any early signs of hypercoagulation. Until nine hours after the start of the operation, the Sonoclot and TEGt tests indicated a hypocoagulative response, probably reflecting dextran effects. A study with 70 patients undergoing THR, a preoperative single bolus of TA (15mg/kg) significantly reduced postoperative bleeding with no reported increase in echo-Doppler verified thrombo-embolic complications compared with control patients without TXA therapy.[29,34]

Although in a meta-analysis, Cid and Lozano reported the reduction in risk of receiving a blood transfusion was independent of the total dose of TEA given. The biological half-time of TXA is about 3.5 h in the serum and about 3 h in the joint fluid. The literature suggests that the TXA is most effective once it is given before the incision. Moreover, the fibrinolytic response after trauma is biphasic with an increased activity during the first hours, followed by a shutdown that peaks at about 24 hours. Thus, suppression of fibrinolysis from the beginning of the operation may be more effective than only at the time of the peak of hyperfibrinolysis later.[35,36]

The duration of tourniquet time and timing of its deflation is also important. In knee surgery, inflation of the pneumatic tourniquet is the powerful initiator of fibrinolysis, whereas, in THR, fibrinolysis is induced by the surgical incision. In THR, antifibrinolytic therapy should be started before the surgical incision and the bleeding is more if the tourniquet is deflated intraoperatively. Hence the prolonged use of a tourniquet can increase the blood loss as increased fibrinolysis is associated with tourniquet use.[3,28,37]

The most commonly used protocol of TXA reported in the literature is two doses of 10 mg per kg body weight is given 3 hours apart. This was a difficult protocol to institute as the second dose would be due at the time when the patient was being discharged from the postoperative recovery room back to ward and therefore either would be forgotten or delayed.

Authors therefore planned one 20-mg per kg intraoperative dose of TEA in patients having primary THA or TKA which would decrease perioperative blood loss and red cell transfusion rates and decrease cost. Benoni et al have also noticed that the therapeutic level of the TXA is maintained only for 3 hours, but with a larger dose (20mg/kg) the level is maintained for 8 h. The temperature of the theatre is generally kept lower, around 20 degrees in joint replacement surgeries. Such a low temperature can also impact coagulation parameters as it may lead to hypothermia, platelet dysfunction, coagulation abnormalities and increases perioperative bleeding.[38]

Coagulation parameters indicated a more active coagulation response with normalization of time to peak and a slight hyperactive trend with (nonsignificant) higher R1 and lower activated coagulation time on the morning of the first postoperative day as compared with preoperative values. In the thromboelastogram from the TEGt, only in TXA patients remained unchanged as compared with preoperative values, whereas in both groups on day one the other measured variables indicated an overall hypoactive response. In conclusion, the IV administration of TXA started before THR decreased the perioperative bleeding to 65% compared to the control group. This is probably by reducing induced fibrinolysis as shown by a decreased D-dimer and increased PAP in the TA group.

Poeran et al, Shown advantages, safety, and efficacy of TXA in 872,416 patients from 510 hospitals in the United States who underwent total hip or knee arthroplasty. They reported statistically significant reduction in blood transfusion (7.7% vs. 20.1%, P<0.001), thromboembolic complications (0.6% vs. 0.8%, P=0.0057), need for mechanical ventilation (0.1% vs. 0.2%, P=0.0003), lower hospital stay cost P<0.001 and admission to an intensive care unit (3.1% vs. 7.5%, P<0.001).[37]

One other important aspect seems to be the economical advantage of TXA in the orthopedic patient, that it reduces the overall hospital costs associated with total hip

or knee arthroplasty. There is a huge increase in total joint arthroplasties in the United States as an increase in aging population is happening not only in the US but all over the world. Hence an economically efficient approach to joint arthroplasties is need of the hour.

Multiple studies reported a decrease in perioperative myocardial infarction, rupture of coronary artery plaques as well as platelet activation due to a reduction in surgical bleeding. This was possible because these drugs prevent fall in hematocrit, avoid tachycardia and hence help in better myocardial oxygen supply.[6,39]

Limitation of this study was as that there was no control group, but we compared our results with previous similar studies. As we mentioned coagulation profile is impacted by a lot of other parameters like cement, the temperature of OT and hematocrit of patient itself.

CONCLUSION

TXA's biggest advantage is that this drug is time tested and proven by various clinical trials in different clinical scenarios. This drug being economical and safe is useful. There is tremendous, evidence-based clinical improvement in its ability to improve overall patient coagulation profile, which reduces hospital stay and costs in joint replacement surgeries like total hip or knee arthroplasty. Their use in joint replacement surgeries reduced the incidence of perioperative myocardial infarction, reduction in surgical bleeding and haematocrit.

Monitoring of coagulation profile shows significant changes of coagulation parameters like platelet function, clot formation and retraction rate, fibrin formation, and fibrinolysis. So, monitoring of coagulation parameters can be useful, to predict the blood loss and complications in patients undergoing joint replacement surgeries in which pneumatic tourniquet and cement is used. Incidence of bleeding in TKR is also high in these settings, hence this monitoring definitely will act as guide for therapeutic intervention in perioperative period.

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