Administration of tranexamic acid in total knee arthoplasty does not increase the risk of deep vein thrombosis and pulmonary embolism

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Abstract
Purpose:
To investigate the effect of application of Tranexamic acid just prior to tourniquet deflation on postoperative D-dimer levels of Total Knee Arthroplasty patients so as to allow precise prediction of DVT and PE.
Method:
A total of 40 patients were identified to undergo primary unilateral total knee arthroplasty. One group of patients received tranexamic acid and second group of patients received a similar volume of normal saline, just before the deflation of the tourniquet. All patients were screened for coagulation parameters before and 24 hours after the surgery. Then the post-operative levels of coagulation parameters of Tranexamic acid group and control group were compared in order to evaluate the effect of Tranexamic acid on these variables.
Results:
The two groups were comparable in pre-operative concentrations of D-dimer levels. The difference between the post-operative D-dimer levels of two groups were statistically significant ($p < 0.05$). D-dimer levels in control group were on the higher side ($p<0.05$) when compared to the TXA group. There were no significant differences in the post-operative values of fibrinogen levels, prothrombin time,thrombin time and activated partial thromboplastin time between the two groups（$p>0.05$).

Conclusion:
The administration of TXA in TKA reduces plasma D- dimer levels and hence reduces the chances of DVT and PE.

Keywords: Total Knee Arthroplasty (TKA),Tranexamic acid (TXA), D-dimer, Deep venous thrombosis (DVT), Pulmonary embolism (PE)

INTRODUCTION

Total knee replacement is a frequently done procedure in modern day practice of any Orthopaedics unit. Total knee arthroplasty (TKA) is usually associated with marked post-operative blood loss [1]. Limiting blood loss both post-operatively and intra-operatively presents a challenge to the surgeon. Blood loss is inevitable during total joint arthroplasty and is influenced predominantly by the type of procedure and patient - related factors [2].Different techniques can be used to reduce the risk of perioperative allogenic blood transfusion in orthopaedic surgery such as preoperative autologous blood donation, intra and postoperative red blood cell salvage, controlled hypotension, normovolemic haemodilution, or lowering the transfusion trigger. These techniques have several disadvantages: they are time consuming, expensive devices are needed, or the risk of poor blood quality increases, especially if using postoperatively salvaged but untreated blood [3].

Tranexamic acid (TXA) is a widely used to reduce the postoperative blood losses and transfusion requirements in a number of types of surgery. It is a synthetic analog of the amino acid lysine and inhibits fibrinolysis locally, without any effect on the fibrinolysis in the plasma from peripheral venous circulation [4]. Previous studies in orthopaedic and urologic surgery have shown that TXA reduces postoperative, but not perioperative blood loss [5,6]. TXA inhibits fibrinolysis by blocking the lysine-binding sites of plasminogen and prevents the degradation of fibrin [7] thus causing a marked reduction in post-operative bleeding. However there are still some doubts about its use as it may act by preventing the breakdown of already formed blood clot by interfering with fibrinolysis [7], and theoretically speaking causing increase in clot load and in turn DVT and PE. Numerous studies have investigated the incidence and prediction of DVT/PE after TKA, especially in patients with osteoarthritis (OA) [8-10]. 90.4% of fatal or near fatal complications, including DVT/PE, have been reported to occur within the first four postoperative days after TKA [11]. Hence it becomes imperative to predict the occurrence of DVT/PE as early as possible to ensure safe rehabilitation.

We therefore investigated the possibility that whether or not Tranexamic acid increases the chances for DVT in Total knee arthroplasty patients. Since Plasma D-dimer measurement has been widely used for screening of DVT/PE [12,13] and D-dimer level correlates with the

incidence of DVT, we thus compared the post-operative D-dimer levels of Tranexamic acid group (n=20) with the Control group(n=20) and evaluated the effect of TXA on D-dimer levels. To avoid fibrinolytic inhibition during this phase of the operation and to exploit the effect of TXA maximally in the post-operative phase, we decided to delay the administration of tranexamic acid in the present study until the end of the operation, when the cement had cured, the arthroplasty had been repositioned and first layer has been closed just before the deflation of the tourniquet. It was found that administration of Tranexamic acid decreases the post-operative D-dimer levels as compared to the patients in control group. There were no significant differences in the post-operative values of fibrinogen levels, prothrombin time, thrombin time and activated partial thromboplastin time between the two groups. Our findings show that Tranexamic acid does not elevate the occurrence of DVT or PE and thus may be administered to reduce the postoperative blood loss in Total Knee Arthoplasty.

MATERIALS AND METHODS

Patient Selection, Preparation and Grouping

40 patients scheduled for elective primary unilateral TKA for osteoarthritis were selected for the study. All the patients had been requested to cease taking any non-steroidal anti-inflammatory agents (NSAIDs) for one week before surgery. All patients were evaluated in preanaesthesia visit a day prior and were advised premedication rantidine 150 mg orally a night prior and day of surgery in the morning. Intravenous access was achieved in operation theatre with 22G intravenous catheter and all patients were preloaded with normal saline 500 ml prior to general anaesthesia.

Exclusion criteria were as follows: (i) history or evidence of coagulopathy and bleeding disorders, (ii) renal dysfunction, (iii) current use of antiplatelet medication and anticoagulants, (iv) acute infection, (v) history of malignancy or coronary artery disease and (vi) thromboembolic event, 1 year prior to surgery, (vii) haemoglobin less than 8 g/dl. (viii) Pregnancy.

Total number of patients (n=40) were randomly divided into two groups (Table 1). TXA group (n=20) received Tranexamic acid 10 mg/kg intravenous, in the time gap of closure of the first wound layer and deflation of the tourniquet while the control group (n=20) received normal saline (placebo) at the same time.

Table 1 Demographic data of the patients

Groups	Gender	Age (years)
TXA Group	Male: 3 Female:17	61.3±.6
Control Group	Male:5 Female:15	*64.7±6.2*

All data expressed as (mean±SD), except for gender ,TXA =tranexamic acid

Surgical techniques and treatment strategy

Preoperative measures included an examination of global coagulation variables, such as (Activated partial thromboplastin time, Prothrombin time, Thrombin time, Fibrinogen levels,D-dimer levels etc.) for deviations from the standard.

Of the total number of patients, 20 Patients were allowed to acclimatize for at least 10 min in the supine position in a quiet operating room at an ambient temperature. The radial artery was cannulated with a 22-guaze catheter, and after 10 minutes, the baseline beat-to-beat electrocardiography (ECG) and arterial blood pressure (BP) signal were recorded for 5 minutes before administration of any sedatives. . Tracheal intubation was facilitated by infusion of atropine 0.01mg/kg. Remifentanil was continuously infused at 0.15 µg/kg/min until the trachea was intubated.

Induction and maintenance of anesthesia were performed in a standardized manner in all patients. Anesthesia was induced with etomidate 0.3 mg/kg as a bolus and maintained with Propofol and Remifentanil infused at an average rate of 2.5mg/kg/hr and 0.2ug/kg /min respectively. All the operations were performed in a bloodless field. A midline skin and medial parapatellar capsular incisions were made to expose the knee joint. After elevation of the limb and exsanguination with an Esmarch bandage, a tourniquet was inflated to 400 to 450 mmHg. At the end of the operation, the tourniquet was deflated and major bleeding was controlled. The cemented Omnifit 7000 series total knee prosthesis was used in all cases and inserted according to the manual supplied by the manufacturer (Stryker, Howmedica osteonics,France). Radiopaque bone cement containing gentamicin (Refobacin Bone cement R) was used for fixation of the cemented arthroplasties (Fig. 1a-e). Any variation in surgical methods, such as synovectomy, soft-tissue release and plugging the femoral canal was recorded.

The study drug was administered intravenously at a dose of 10 mg/kg, just before deflation of tourniquet. A compressive bandage was applied after closing the wound in layers and a vacuum suction drain was placed before deflation of tourniquet. Whole blood was administered if the blood loss was more than 15% of the body weight or postoperatively haemoglobin (Hb) was <8 g/dl or haematocrit <30%. Continuous passive motion exercise was started on the first or second postoperative day according to the patient's general condition. Patients were encouraged to perform active ankle and foot exercise as early as possible after surgery. All patients were allowed to walk with weight-bearing as far as could be tolerated. The suction drain was removed within 72 post-operative hours.

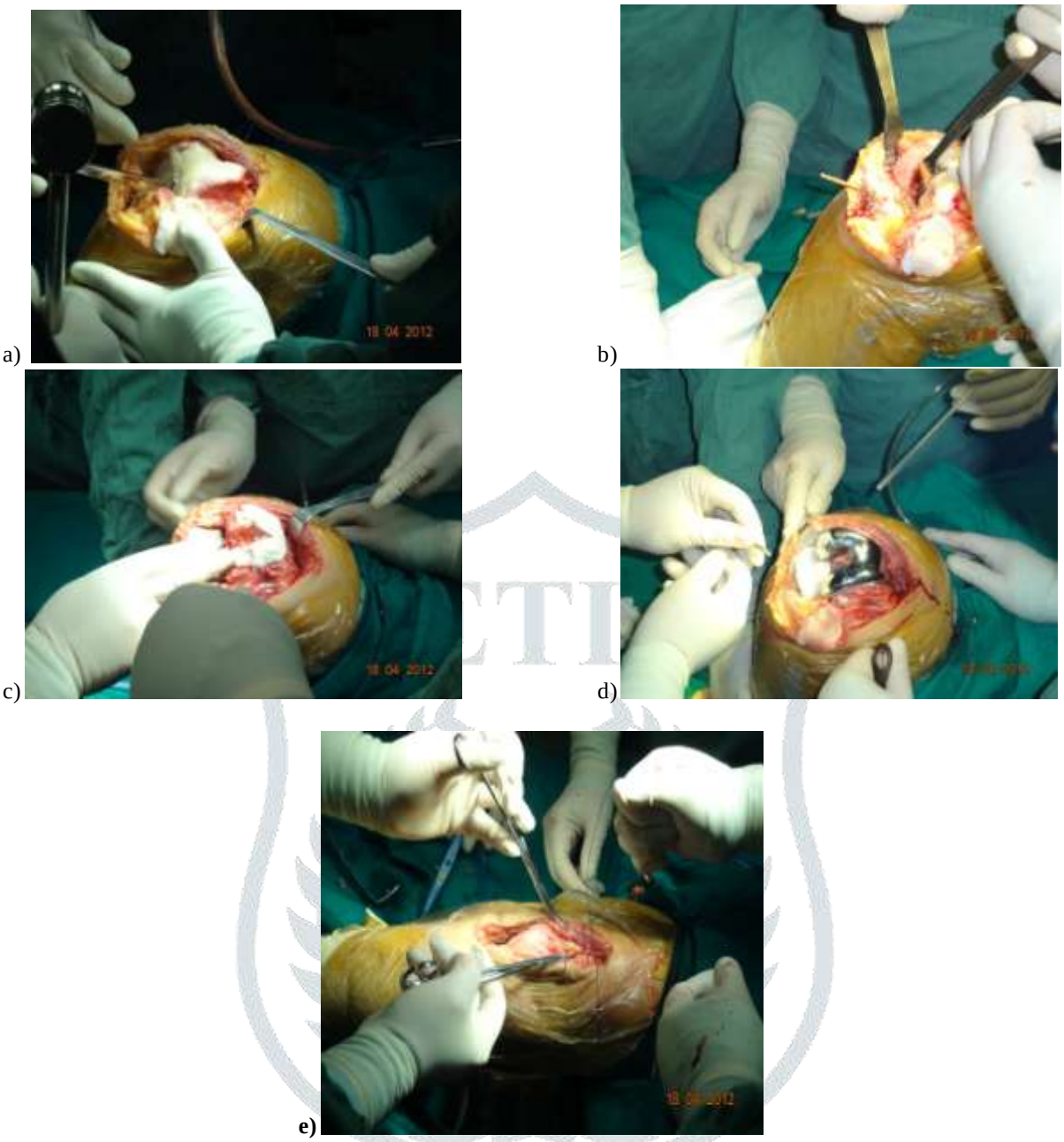


Fig 1. a Preparation of Femoral end. **b** Preparation of Tibial end. **c** Cementing of prosthesis. **d** Implantation of Prosthesis (femoral component). **e** Closure of wound layer.

All patients were screened for coagulation parameters such as D-dimer, PT, TT, APTT, Fibrinogen levels 24 hours postoperatively,and the obtained values were compared between tranexamic acid group and the control group in order to evaluate the effect of Tranexamic acid on these variables.

STATISTICS

For tests of differences between quantitative data, two-sided *t*-tests were used. Differences between proportions and qualitative data were tested by the chi-squared test with Yates' correction. In the text, data are presented as mean ± standard deviation (SD) and p values of <0.05 are considered significant.

RESULTS

Both study groups were similar, with no statistically significant differences in demographics, surgical variables, and preoperative laboratory parameters (Table 2-3). The two groups were comparable in preoperative concentrations of D-dimer (Table 2), but the difference between the postoperative D-dimer levels of two groups were statistically significant (Table 3), ($p < 0.05$).

Table 2 Preoperative assessment of the patients

Groups	D-dimer(ug/l)	PT(sec)	APTT(sec)	FIB(g/l)	TT(sec)
TXA	0.243±0.097	9.095±0.747	30.84±3.127	3.006±0.747	14.35±0.941
Control	0.228±0.089	9.375±0.884	29.22±3.991	3.153±0.771	15.06±2.416

All data expressed as mean ±SD, PT=Prothrombin time,APTT= Activated partial thromboplastin time, ,FIB= Fibrinogen,TT=Thrombin time,TXA= tranexamic acid

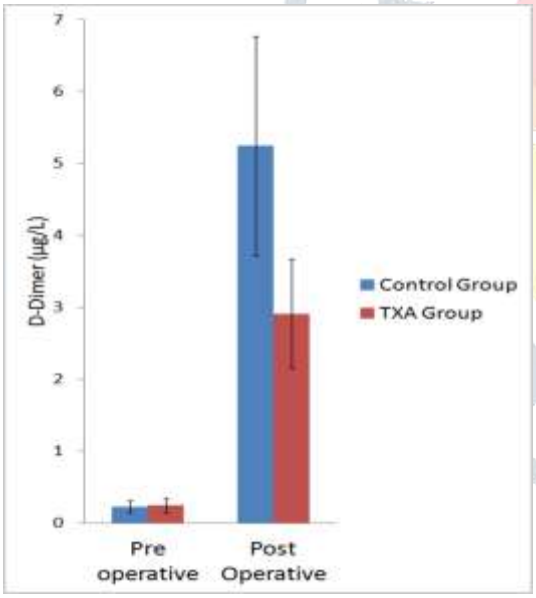
Table 3 Post-operative assessment of the patients

Groups	D-dimer(ug/l)	PT(sec)	APTT(sec)	FIB(g/l)	TT(sec)
TXA	2.914±0.764	9.588±1.046	28.62±2.209	3.0±0.735	14.40±1.634
Control	5.249±1.526	10.01±1.076	28.74±2.891	2.852±0.681	14.98±1.856

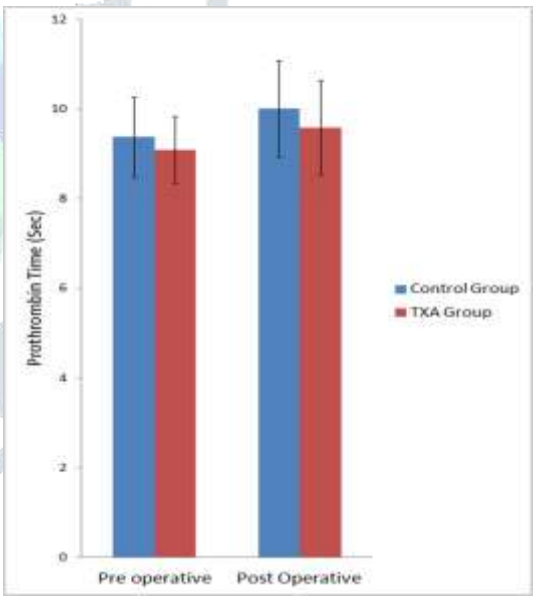
All data expressed as mean ±SD , PT=Prothrombin time, APTT= Activated partial thromboplastin time,FIB= Fibrinogen,TT=Thrombin time,TXA= tranexamic acid

D-dimer levels in Control group [5.249±1.526] was on the higher side ($p<0.05$) when compared to the TXA group [2.914±0.764]. In Control Group the post-operative fibrinogen levels [2.852±0.681] were on the lower side when compared to preoperaive values [3.153±0.771] but in Tranexanic acid group the preoperative [3.006±0.747] and the postoperative [3.0±0.735], fibrinogen levels were almost equal ,this difference in groups however was not statistically significant ($p>0.05$). There were no significant differences in the values of Prothrombin time (PT), Thrombin time (TT) and Activated partial thromboplastin time (APTT) between the two groups（$p>0.05$). The data is represented graphically in the figure 2.

a)



b)



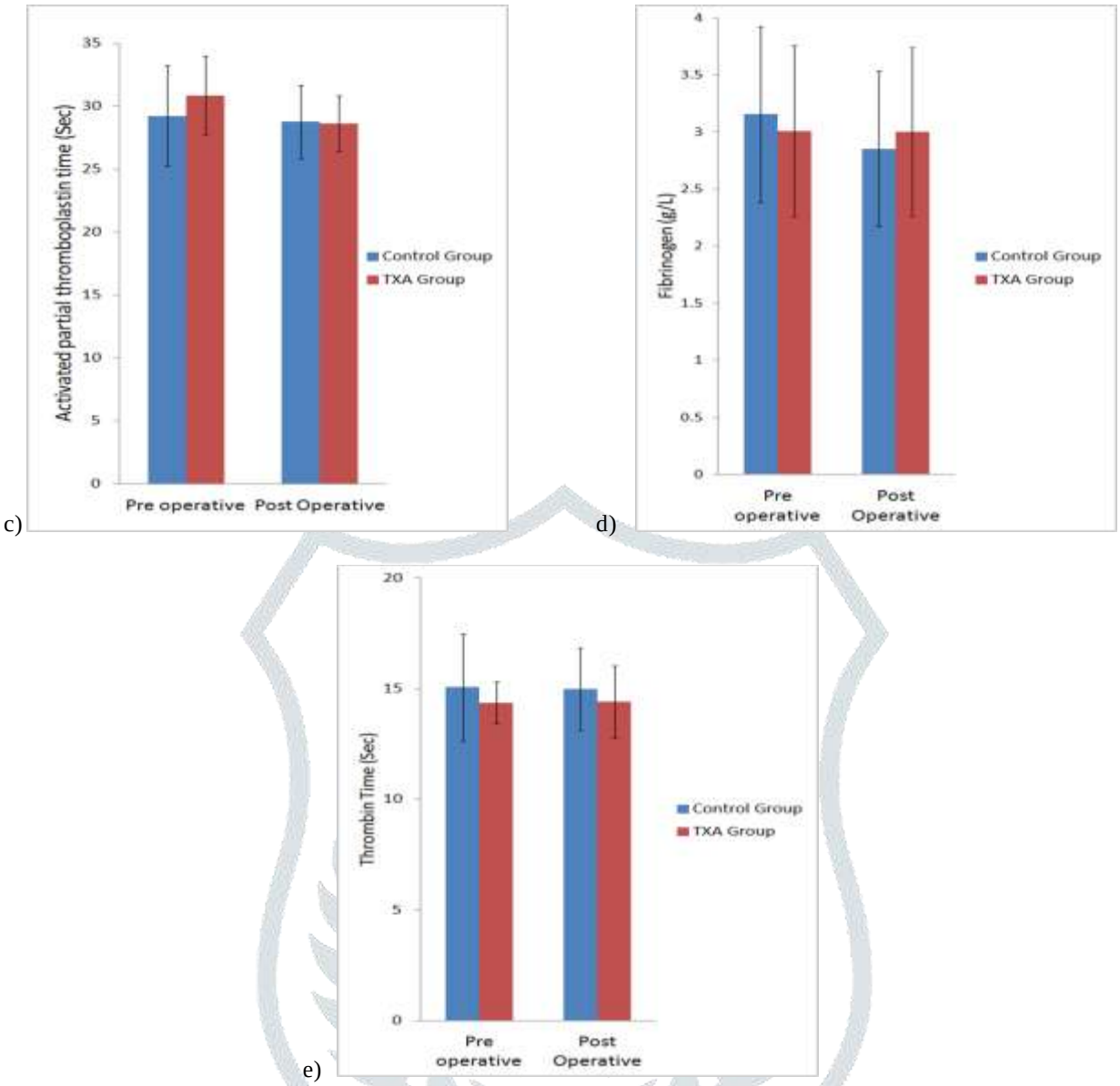


Figure 2 : Pre-operative and Post-operative, **a**) D-dimer ; **b**)PT ; **c**) APTT ; **d**)Fibrinogen ; **e)** TT in TXA group and Control group .

DISCUSSION

Various antifibrinolytic agents such as, aprotinin, e-aminocaproic acid, and Tranexamic acid (TXA) can help reduce blood loss in TKA. Of these TXA is preferred as it is cheaper and less allergenic than aprotinin and is more potent than e-aminocaproic acid. Tranexamic acid is a haemostatic agent and acts by competitively inhibiting the activation of plasminogen to plasmin. It also blocks the binding of plasminogen to fibrin, which retards fibrinolysis, thus reducing blood loss by clot stabilization rather than promotion of clot formation . Since TXA inhibits fibrinolysis, therefore the its administration causes concern for an increase in the incidence of thrombo-embolic events like DVT and PE, associated with most of the antifibrinolytic agents. It was reported that a large proportion (perhaps one half) of DVT/PE cases occurred between the intraoperative period and the first three postoperative days, although many of these cases resolved spontaneously, approximately half within 72 h [14]. It was also demonstrated that 90.4% of life-threatening complications including PE resulting from lower-extremity total joint arthroplasty occurred within 4 days of index surgery [15]. Thus, it is extremely important to check for the clinical signs of DVT/PE carefully within the first four postoperative days.

In this study the possibility of DVT resulting due to trenexamic acid administration in Total knee arthroplasty patients was evaluated by screening the plasma of patients for D-dimer levels. TXA was administered at a dose of 10 mg / kg of TXA, to obtain the desired antihemorrhagic effect [12]. TKA surgery is mainly performed with a tourniquet in situ; therefore, intra-operative blood loss can be minimal. Hence, TA was given just prior to tourniquet deflation or at the time of wound closure, so that it acts post-operatively. One of the strong points of our study is that the point of timing of administration of TXA was kept constant in all patients. As the time from closure of the first wound layer to release of the tourniquet is fairly constant, we felt this was a reliable time to administer the drug in all the cases. Thus the timing of the effect of TXA on the fibrinolytic response to surgery and tourniquet release was kept almost constant in all the patients.

The study involved 40 patients randomly divided into two groups (i) TXA group (n=20) received Tranexamic acid 10 mg/kg intravenous, in the time gap of closure of the first wound layer and deflation of the tourniquet while the (ii) control group (n=20) received normal saline (placebo) at the same time. Patients in both the groups were screened for coagulation parameters such as D-dimer, PT, TT, APTT, Fibrinogen levels 24 hours postoperatively and the obtained values were compared between tranexamic acid group and the control group in order to evaluate the effect of Tranexamic acid on these variables. The results indicated that administration of tranexamic acid decreases the plasma D-dimer levels post-operatively (2.914$\pm$0.764 in TXA group vs 5.249$\pm$1.526 Control group). There were no significant differences in the values of Prothrombin time (PT), Thrombin time (TT) and Activated partial thromboplastin time (APTT) between the two groups. Thus we concluded that tranexamic acid has negative effect on post operative D-dimer levels, when administered prior to deflation of tourniquet in Total knee arthroplasty. This in turn implies that tranexamic acid does not elevate the occurance of DVT or PE during early post-operative period, which is indicative by lower levels of D-dimer.

REFERENCES

[1] K.R Sehat, R.L Evans and J.H Newman, "Hidden blood loss following hip and knee arthroplasty. Correct management of blood loss should take hidden loss into account." J Bone Joint Surg Br, 2004, 86:561-5.

[2] P. Narayana, V. Padmanabhan, and A. Mullaji, "Blood Loss in total knee arthroplasty: an analysis of risk factors.", International Orthopaedics, 2007, 31:39-44.

[3] C.D. Krohn, O. Reikeras, S. Bjornsen and F. Brosstad, "Fibrinolytic activity and postoperative salvaged untreated blood for autologous transfusion in major orthopaedic surgery.", Eur J Surg, 2001,16:168-72.

[4] J.C. Alvarez, F.X. Santiveri, I. Ramos, E. Vela, L. Puig and F. Escolano, "Tranexamic acid reduces blood transfusion in total knee arthroplasty even when a blood conservation program is applied." ,Transfusion, 2008, 48:519-25.

[5] G. Benoni, S. Bjorkman and H. Fredin, "Application of pharmacokinetics data from healthy volunteers for the prediction of plasma concentrations of tranexamic acid in surgical patients.", Clin Drug Invest, 1995, 10:280-7.

[6] G. Benoni and H. Fredin, "Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty: a prospective, randomised, double-blind study of 86 patients." J Bone Joint Surg [Br], 1996, 78-B:434-40.

[7] I.M. Nilsson, "Clinical pharmacology of aminocaproic and tranexamic acids." J Clin Pathol Suppl R Coll Pathol, 1980, 14:41-7.

[8] C. Kearon, "Duration of venous thromboembolism prophylaxis after surgery.", Chest, 2003,124:386S–92.

[9] M.J. Maynard, T.P. Sculco and B. Ghelman "Progression and regression of deep vein thrombosis after total knee arthroplasty." Clin Orthop Relat Res, 1991, 1:125–30.

[10] R.L. Schiff, S.R. Kahn, I. Shrier, C. Strulovitch, W. Hammouda, E. Cohen and D. Zukor, "Identifying orthopedic patients at high risk for venous thromboembolism despite thromboprophylaxis.", Chest, 2005, 128:3364–71.

[11] J. Parvizi, A. Mui, J.J. Purtill, P.F. Sharkey, W.J. Hozack and R.H. Rothman, " Total joint arthroplasty: when do fatal or near-fatal complications occur?", J Bone Joint Surg Am, 2007, 89:27–32.

[12] J. Kelly and B.J. Hunt. "A clinical probability assessment and D-dimer measurement should be the initial step in the investigation of suspected venous thromboembolism.", Chest, 2003, 124:1116–9.

[13] P.D. Stein, R.D. Hull, K.C. Patel, R.E. Olson, W.A. Ghali, R. Brant, R.K. Biel, V. Bharadia and N.K. Kalra, "D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review.", Ann Intern Med, 2004, 140:589–602.

[14] C. Kearon. "Duration of venous thromboembolism prophylaxis after surgery." Chest, 2003, 124:386S–92.

[15] J.L. Parmet, J.C. Horrow, R. Singer, A.T. Berman and H. Rosenberg, "Echogenic emboli upon tourniquet release during total knee arthroplasty: pulmonary hemodynamic changes and embolic composition**.",** Anesthesia & analgesia, 1994, 79(5):940-945.