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Original Article

The prophylactic role of tranexamic acid to reduce blood loss during radical surgery: A prospective study

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Abstract

Background: The radical surgical procedures are associated with perioperative blood loss. This study was aimed to evaluate the clinical efficacy and safety of tranexamic acid in reducing perioperative blood loss in patients undergoing radical surgery.

Materials and Methods: Sixty ASA class I and II adult consented female patients, scheduled for elective radical surgery and met the inclusion criterion, were blindly randomized into two groups to receive either intravenous 1 g tranexamic acid 20 min before skin incision or an equivalent volume of normal saline as placebo (P). All patient's total blood loss was measured and recorded perioperatively at the 12th h postoperatively. The preoperative and postoperative hemoglobin, hematocrit values, serum creatinine, activated thromboplastin time, prothombin time, thrombocyte count, fibrinogen, D-dimer, and symptoms of pulmonary embolism were comparatively evaluated.

Results: The tranexamic acid significantly reduced the quantity of total blood loss, 576 ± 53 mL in study group as compared to 823 ± 74 mL in the control group (P<0.01). Postoperatively hematocrit values were higher in the tranexamic acid group. The coagulation profile did not differ between the groups, but D-dimer concentrations were increased in the control group. No complications or adverse effects were reported in the either group.

Conclusion: The prophylactic administration of tranexamic acid has effectively reduced theblood loss and transfusion needs during radical surgery without any adverse effects or complication of thrombosis.

Key words: Antifibrinolytic agent, coagulation profile, hematocrit values, tranexamic acid

INTRODUCTION

The radical surgical procedures are associated with excessive perioperative blood loss and necessitate the blood transfusion in the absence of blood conservation strategies. Surgery affects the coagulation systems and the fibrinolytic system shuts down due to increased release of plasminogen activator inhibitor.[1] Blood transfusions are known to increase complications and morbidity. In order to reduce the amount of bleeding during radical surgery, the technical operative measures and antifibrinolytic agents are required to improve hemostasis.[2]

Antifibrinolytic agents in current use include the naturally occurring serine protease inhibitor aprotinin, the synthetic protease inhibitor nafamostat and the synthetic lysine analogues epsilon aminocaproic acid and

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tranexamic acid.[3] Lysine analogues reversibly bind to the lysine binding site on plasminogen, thereby inhibiting the conversion of plasminogen into plasmin on the surface of fibrin. Tranexamic acid is a competitive inhibitor of plasminogen activation. The intravenous tranexamic acid has been shown to be very useful in reducing blood loss hence blood transfusion during coronary artery bypass, spinal surgery, maxillofacial surgery, orthotopic liver transplantation and total hip or knee arthroplasty.[4-9]

This study was aimed to evaluate the clinical efficacy and safety of tranexamic acid to reduce the blood loss and on the coagulation and fibrinolysis profile during radical surgery.

MATERIALS AND METHODS

After approval from Institution Ethical Committee and written informed consent, 60 adult female patients of 38 to 68 years of ASA class I and II, scheduled for either elective modified radical mastectomy or total abdominal hysterectomy (wertheim's operation), were enrolled for the present prospective randomized control double blind study, carried out from October 2010 to June 2011. Exclusion criterion were known allergy to medication (tranexamic acid), anemia, preoperative hepatic or renal dysfunction, serious cardiac or respiratory disease, congenital or acquired coagulopathy or a history of deep vein thrombosis/thromboembolic disease.

Patient's randomization was done by the rule of odds and even into two groups of 30 patients each to receive either 1 g tranexamic acid as slow intravenous bolus (TXA) 20 min prior to skin incision or equal volume of normal saline as placebo (P) in the double blind manner. Both the surgeon and anesthetist were blinded to the treatment regimen. Tranexamic acid injection was prepared by diluting 1 g (10 mL) tranexamic acid with 20 mL of 5% glucose.

After arrival to operation theater, the routine monitoring for ECG, peripheral pulse oximetry and noninvasive blood pressure was established and ringer lactate solution was started. Premedication of metoclopramide (10 mg), glycopyrrolate (0.2 mg), midazolam (2 mg), and fentanyl (1.5 μg·kg^{1}) was given and anesthesia was induced with propofol 2 mg·kg^{1} till loss of verbal command and tracheal intubation was facilitated with vecuronium 0.1 mg kg^{1}. The anesthesia was maintained with isoflurane and a mixture of nitrous oxide with 40% oxygen with increments of fentanyl and vecuronium. The arterial blood pressure, heart rate, ECG, end tidal carbon dioxide concentration, and peripheral pulse oximetry were measured continuously. If patients had sign of hemodynamic instability due to blood loss (heart rate >120 beats/min or a systolic blood pressure decrease by more than 20% of base value) despite adequate volume replacement, blood transfusion was given. The mean arterial blood pressure was maintained during surgery. After surgery the residual neuromuscular block was antagonized with appropriate doses of neostigmine (0.05 mg·kg^{-1}) and glycopyrrolate (0.01 mg kg^{1}) and extubation was performed when respiration was adequate. The patients were transferred to postanesthesia care unit for further observation.

Intraoperative quantity of blood losses were measured by weighing swabs, sponges, operative drapes and measuring the volumes in the suction bottles after surgery and by measuring the drain collectors in post anesthesia care unit.

All patients' preoperative and 12th hour postoperative blood samples were analyzed for hemoglobin, hematocrit, platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), serum creatinine, fibrinogen, D-dimer and symptoms of pulmonary embolism such as dyspnea, hemoptysis, pleuritic chest pain, apprehension, tachypnea, tachycardia, rales etc. Doppler ultrasound of lower limbs was done daily in all patients for signs of deep vein thrombosis (DVT).

The data obtained in the study are presented in tabulated manner and expressed as mean±SD. Statistical analysis was performed using Microsoft Excel and Stat graphic plus for windows. Time related variables were analyzed using paired *t*-test and Wilcoxon test. The differences in variables related to time and coagulation values were analyzed with Chi square test and fisher exact test. A *P* value of <0.05 was considered statistically significant.

RESULTS

There was no significant difference in demographic data between groups. No significant difference was present between groups in mean hemoglobin, hematocrit, platelet count, fibrinogen values, and coagulation parameters. All radical surgeries were done under general anesthesia and standardized anesthetic technique was used for all patients of both groups [Table 1].

No significant difference was found between groups in mean hemoglobin, hematocrit, platelet count, fibrinogen values and coagulation parameters. The total measured blood loss (576 ± 53 mL) in tranexamic acid group was significantly less than control group (823 ± 74 mL) ($P<0.01$). The need for blood transfusion was more in the control group. Only two patients in tranexamic acid group required allogeneic blood transfusion (Group TA 2 versus 15 of Group P) [Table 2]. Intraoperatively, the amount of crystalloid solution used for fluid replacement was comparable between the groups.

There were no clinically relevant differences in the vital signs in patients following tranexamic acid administration and no thromboembolic complications were detected in either group during hospitalization.

Table 1: Demographic profile, preoperative hemoglobin and coagulation parameters

Parameters	Group P	Group TA
Age (years)	46.3 ± 18.2	47.9 ± 13.1
Weight (kg)	74.5 ± 11.4	78.4 ± 12.7
ASA physical status I/II	13/17	16/14
Type of surgery		
Modified radical mastectomy	13	17
Wertheim's operation	14	16
Duration of surgery (min)	135.4 ± 23.5	129.7 ± 21.4
Mean arterial blood pressure during surgery (mm Hg)	82.5 ± 8.7	85.3 ± 6.9
Hemoglobin (g dL^{-1})	12.4 ± 2.8	12.1 ± 2.5
Hematocrit (%)	36.12 ± 1.5	35.26 ± 2.1
Platelet count (x10^3 u/L)	309.36 ± 42	284.72 ± 44
Prothrombin time (sec)	12.8 ± 1.1	13.1 ± 0.8
aPTT (sec)	13.9 ± 0.8	14.1 ± 2.1
Fibrinogen (mg dL^{1})	383.72 ± 42	385. 04 ±57

Table 2: Comparative values of measured blood loss, blood transfusions, hemoglobin and coagulation profile

Parameters	Group P	Group TA
Measured blood loss (mL)	823 ± 74	576 ± 53
Blood transfusions (n)	15	2
Hemoglobin (gm·dL^{-1})		
Preoperative	12.4 ± 2.8	12.1 ± 2.5
Postoperative	09.8 ± 1.3	10.6 ± 1.5
Hematocrit (%)		
Preoperative	36.12± 1.5	35.26 ± 2.1
Postoperative	29.36 ± 1.8	30.14 ± 2.2
Platelet count (x10^3 u/L)		
Preoperative	309.36 ± 42	284.72 ± 44
Postoperative	264.46 ± 34	273.42 ± 35
Prothrombin time (sec)		
Preoperative	12.8 ± 1.1	13.3 ± 0.8
Postoperative	13.9 ± 0.8	14.1 ± 2.1
aPTT (sec)		
Preoperative	32.1 ± 4.3	31.5 ± 4.6
Postoperative	34.9 ± 4.9	32.9 ± 3.7
Fibrinogen (mg dL^{1})		
Preoperative	393.72 ± 42	385.04 ± 57

DISCUSSION

This study has evaluated the efficacy and safety of tranexamic acid to decrease blood loss during radical surgery. Hemostasis depends on a successful balance between the coagulation, complement and fibrinolytic pathways with complex interactions between plasma protein, platelets, blood flow and viscosity and the endothelium. Injury to the arterial or venous wall exposes perivascular, tissue factor-expressing cells to blood.[10] Bleeding can increase the duration of hospital stay, re-operations and necessitate blood transfusion to restore blood loss and to reduce the morbidity after such operations. The risk of hemolytic reaction, anaphylaxis, acute lung injury and infection transmission, are associated with blood transfusion. Transfusion can have potential of adverse immune consequences and end organ effects. Moreover, it is a potentially scarce and expensive resource. In this study, the prophylactic administration of tranexamic acid has shown significant decrease in total measured blood loss during radical surgeries and has reduced the need of blood transfusion.

There are both theoretical reasons and clinical data suggesting that reduction of perioperative blood loss may improve the surgical outcome as less bleeding will be able to provide better operating field hence less surgical time.[10] Primary hyperfibrinolysis that occurs during surgery plays a significant role in blood loss and is the basis for the use of antifibrinolytic agents to reduce perioperative blood loss and transfusion requirements. Antifibrinolytic drugs, epsilon aminocaproic acid (EACA), aprotinin, and tranexamic acid have shown to decrease bleeding of major surgical procedures.[3] The aprotinin is an expensive medication and can cause anaphylaxis, obstructive uropathy thrombosis in glomerular capillaries, rhabdomyolysis, and myoglobulinuria.[11]

The preincisional use of tranexamic acid has been reported to decrease bleeding in cardio-pulmonary bypass surgery,[5] total hip arthroplasty,[12,13] knee arthroplasty,[14-16] and cesarean operations.[17-19] However, when it is given intraoperatively it does not decrease bleeding because fibrinolytic activation is a cascade process that is most easily inhibited in its earlier phase.[1,2] Benoni and colleagues found no benefit from administration of tranexamic acid after release of the tourniquet and stated that for optimum efficacy tranexamic acid should be administered prophylactically at an earlier stage.[14]

Our data confirmed that tranexamic acid treated patients showed decrease in blood loss. It has not induce platelet activation, indeed the platelet count were similar in both groups. Extrinsic coagulation (PT) and the intrinsic pathway of coagulation (aPTT) were unaffected by tranexamic acid and has ranged within their reference limits.

Celebi *et al*. recommended the use of tranexamic acid administration for decreasing the need for blood transfusion in gynecologic cancer surgery, in view of the negative effects of blood transfusions.[20] Lemay *et al*. concluded that tranexamic acid have not shown changes in the measured blood loss but has reduced the red blood cell transfusion requirements in patients undergoing primary total hip replacement surgery.[13] Wu *et al*. examined the feasibility of a blood transfusion free hepatectomy by administration of TXA 500 mg preoperatively followed by 250 mg 6 hourly for 3 days

and has observed significantly less intraoperative blood loss, shorter operative time and lower transfusion rate.[17] Chauhan *et al*. reported that epsilon-aminocaproic acid and tranexamic acid are equally effective to decrease bleeding in pediatric cardiac surgery.[21] The use of tranexamic acid in prostatic surgery is not very well studied, although the prolonged oral administration of tranexamic acid (1 g three times every day, orally, for 3 weeks) may reduce the incidence of secondary bleeding. The continued postoperative use of tranexamic acid added no advantages in terms of blood saving and was associated with tendency to renal dysfunction.

D-dimer concentration is not a direct indicator of the plasmin activity but reflects the degradation of fibrin. This study found significantly less number of patients with increased D-dimer concentration in the TXA group while there was increased D-dimer concentration in the control group. This difference indirectly supports the antifibrinolytic effects of tranexamic acid. Despite the efficacy of tranexamic acid for reducing bleeding, Jansen *et al*. found no direct correlation between blood loss and variables of fibrinolysis (D-dimer and fibrinogen degradation products).[22] Ekback *et al*. demonstrated a lower increase in postoperative D-dimers with administration of TXA during total hip replacement.[12] Benoni *et al*. also showed the statistically lower plasminogen concentration ($P<0.001$) in the tranexamic acid group than in the placebo group.[23]

Rapid intravenous administration of tranexamic acid may cause hypotension and should therefore be administered slowly as infusion. In our study, no case of intraoperative thromboembolism was reported with tranexamic acid while in a recent review the incidence of venous thromboembolic events with tranexamic acid was 0.7%, with aprotinin 1.4% and with placebo 1.5%.[24]

CONCLUSION

Tranexamic acid has significantly reduced the amount of total blood loss and need of blood transfusion during radical surgery with no apparent effect on blood coagulation parameters. Its prophylactic use is inexpensive with adequate safe profile.

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