Original Article

Efficacy of Tranexamic Acid in Reducing Perioperative Blood Loss and Blood Transfusion in Primary Malignant Musculoskeletal Tumor Surgery

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Background: Major operations on soft tissue and bone sarcomas are associated with significant blood loss and the requirement for transfusions. There is a sharp increase in mortality rate in patients who receive allogenic blood transfusions and subsequently acquire transfusion-acquired infections. Reducing blood loss and the need for transfusions could potentially reduce that mortality rate. Low doses of tranexamic acid [TXA] may be able to reduce blood loss and transfusion requirements during these operations.

Objective: To study the effect of TXA on perioperative blood loss and blood transfusion requirements in patients undergoing extremity primary bone tumor surgery.

Materials and Methods: Twenty-two extremity primary bone tumor surgery patients were randomized into two groups. The control group received a placebo, and the study group received 2 grams of TXA intravenously followed by intravenous infusion of 1 gram in a drip every 8 hours postoperatively. The volume of intraoperative blood loss, amount of blood transfused, volume of drained blood, hemoglobin levels, and any thromboembolic complications were recorded and assessed.

Results: The mean intraoperative blood loss in the TXA group and the control group were 300 ml and 600 ml, respectively ($p = 0.356$). Volume of drained blood was not reduced in the TXA group compared with control group, but the difference was not statistically significant: 180 mL (0 to 580) vs. 100 mL (0 to 580), respectively. The amount of blood transfused was lower in patients receiving TXA than in the control group: 1 unit (0 to 15) unit vs. 0 units (0 to 5), respectively, but the different was not significant ($p = 0.699$). Decrease of hemoglobin levels was non-significantly lower in TXA group than in the control group: 1.79 g/dL (SD $\pm$1.39) vs. 2.51 g/dL (SD $\pm$1.36) ($p = 0.235$). No thromboembolic complications were detected in either group.

Conclusion: Tranexamic acid has the clinical effect of decreasing blood loss and transfusion requirements in patients undergoing extremity primary malignant musculoskeletal tumor surgery, but the reduction is not statistically significant.

Keywords: Tranexamic acid, Perioperative blood loss, Primary malignant musculoskeletal tumor

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Surgical oncology of soft tissue sarcoma and bone sarcoma is associated with significant perioperative blood loss and blood transfusion. Mortality rates increase considerably in patients who receive allogenic transfusions due to transfusion-acquired infection, higher rates of postoperative infection, intravascular hemolysis, transfusion-induced coagulopathy[1], and renal impairment. Furthermore, since blood transfusion involves additional expense, a reduction in transfusions would be an economic benefit. Several pharmacological and non-pharmacological intervention methods are currently in

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use including preoperative autologous blood donation, acute normo-volumic hemodilution, perioperative blood salvage hypotensive anesthesia, maintenance of normothermia, preoperative embolization, and prophylactic administration of synthetic antifibrinolytic drugs such as tranexamic acid [TXA] which are used to reduce perioperative blood loss and avoid blood transfusion.

TXA is an antifibrinolytic drug, a synthetic lysine analogue, that inhibits the binding of lysine residues on fibrin to plasmin or plasminogen, thus preventing fibrinolysis[2,3]. The efficacy of tranexamic acid in reducing blood loss in knee and hip replacement surgery, spine surgery, and surgical trauma cases has been well established[4-14]. A meta-analysis of 46 randomized controlled trials concluded that tranexamic acid reduced blood loss and transfusion in major orthopedic surgery without increasing the risk of deep venous thrombosis [DVT][4]. A systematic review and meta-analysis of nine studies showed perioperative intravenous TXA reduced blood loss in spinal surgery patients[12]. The efficacy of TXA in reducing blood loss in intralesional tumor excision and instrumentation in the spine surgery, however, has only been reported recently and the findings were not statistically significant[15].

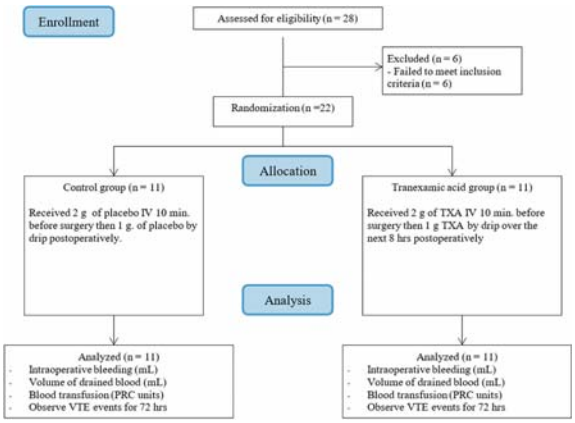

Figure 1. Flowchart of patient recruitment and data obtained during the study.

The intervention hypothesis in this study is that a prophylactic low dose of TXA can reduce blood loss and transfusion requirements during major surgical oncology of soft tissue sarcoma and bone sarcoma. That hypothesis was tested in this prospective, randomized, double-blind study. Perioperative blood loss was measured by volume. The total amount of blood transfused, the volume of drained blood over 48-hours, and the hemoglobin level 24 hours postoperatively were recorded as were thromboembolic complication events.

Materials and Methods

This study was approved by the Research Ethical Committee of the Royal Thai Army Medical Department, and informed consent was obtained from all participants before beginning the study. We performed a prospective, double-blind, randomized-controlled trial which enrolled 22 patients from June 2016 to March 2017 who had a primary malignant

Table 1. Demographic data

Baseline characteristics	Control group n = 11	TXA group n = 11
Sex		
Male, n (%)	5 (45.45)	6 (54.55)
Female, n (%)	6 (54.55)	5 (45.45)
Age (years), mean ± SD	56.64±25.36	48.73±21.67
BMI (kg/m^2), mean ± SD	22.59±2.27	21.85±4.37
Comorbidity		
No, n (%)	5 (45.45)	7 (63.64)
Yes, n (%)	6 (54.55)	4 (36.36)
Preoperative hematocrit (%), mean ± SD	35.54±4.07	35.76±4.15
Preoperative hemoglobin (g/dL), mean ± SD	11.81±1.45	11.72±1.60
Preoperative platelets (cells/mm^3), mean ± SD	282,636.36±124,070.36	286,454.55±106,291.45
PT (sec), mean ± SD	12.61±0.88	12.38±1.07
PTT (sec), mean ± SD	25.61±2.46	23.88±3.10
INR, mean ± SD	1.08±0.08	1.03±0.11

musculoskeletal tumor treated at Phramongkutklao Hospital College of Medicine. The age of the patients was between 18 and 65 years old. The diameter of the tumors was more than 5 cm. measured by MRI, and no embolization was performed before surgery. We excluded patients who had a history of bleeding disorders or thromboembolic disease, a platelet count lower than 150,000 ml^3, an abnormal coagulogram, a known allergy to TXA, a history of anticoagulant drug treatment, a body mass index [BMI] greater than 30 kg/mm^2, Child-Pugh cirrhosis grade B or C, creatinine clearance < 30, or uncontrolled blood pressure >160/90 mmHg. Patients who participated in this study signed an informed consent form before their operation.

Table 2. Baseline clinical information

	Control group n (%)	TXA group n (%)
Diagnosis		
Soft tissue sarcoma	6 (54.55)	9 (81.82)
Bone sarcoma	5 (45.45)	2 (18.18)
Site		
Left	4 (36.36)	7 (63.64)
Right	7 (63.64)	4 (36.36)
Location		
Lower extremity	9 (81.82)	9 (81.82)
Upper extremity	2 (18.18)	2 (18.18)
Tumor staging (enneking)		
IA	-	-
IB	2 (18.18)	2 (18.18)
IIA	-	-
IIB	3 (27.27)	3 (27.27)
III	6 (54.55)	6 (54.55)
Type of surgical margin		
Intralesional	-	-
Marginal	-	-
Wide	11 (100)	11 (100)
Radical	-	-
Type of bone resection		
No	6 (54.55)	8 (72.73)
Intraarticular	4 (36.36)	2 (18.18)
Extraarticular	-	-
Intercalary	1 (9.09)	1 (9.09)
Type of bone reconstruction		
No reconstruction	7 (63.64)	8 (72.73)
Arthrodesis	-	-
Allograft reconstruction	-	3 (27.27)
Autograft reconstruction	1 (9.09)	-
Recycling tumor-bearing autograft	1 (9.09)	-
Allograft composite prosthesis	1 (9.09)	-
Endoprosthesis	1 (9.09)	-
Soft tissue reconstruction		
None	8 (72.73)	9 (81.82)
Skin graft	2 (18.18)	1 (9.09)
Ligament reconstruction	1 (9.09)	1 (9.09)

Patients were randomized into two groups using the block of four method, the research group and the control group. Patients did not know which group they were assigned to. Group codes were concealed in sealed envelopes which were opened by a scrub nurse. Only the pharmacologist knew which group received which drug treatment. Eleven patients in the study group received 2 grams of TXA 10 minutes before surgery followed by intravenous infusion of 1 gram TXA drip over a period of 8 hours postoperatively; the control group received an equivalent volume of placebo. All patients underwent standard surgery for their disease condition carried out by the same surgical team. Intraoperative blood loss was measured by weighting surgical gauzes used in the operative field using a digital scale and the blood from suction drainage. The amount of blood transfused was recorded as the number of units of packed erythrocytes received within the first 24 hours following the operation. In addition, the amount of postoperative blood loss in the surgical drains was recorded at the orthopedics ward. Hemoglobin level was measured before and 24 hours after surgery. Clinical thromboembolic complications such as pulmonary embolism, DVT, and myocardial infarction were noted during the first 72 hours after surgery. Preoperative data, including age, gender, BMI, history of allergy, and comorbidities, were recorded. Laboratory measurements of hemoglobin, hematocrit, platelet count, and coagulogram were conducted in both groups.

The mean intraoperative blood loss in TXA group was 300 ml (range 100 to 1,800 ml) and in the control group was 600 ml (100 to 2,500 ml). There was decreased blood loss (p = 0.356). The mean postoperative volume of drained blood was higher in the TXA group compared with the control group [180 ml (0 to 580 ml) vs. 100 ml (0 to 580 ml)]. The mean number of transfused units (PRC units) was lower in patients receiving TXA than in control group [1 unit (0 to 15) vs. 0 unit (0 to 5); p = 0.699]. The mean hemoglobin decrease 24 hours postoperatively was lower in patients receiving TXA than the control group [1.79$\pm$1.39 g/dL vs. 2.51$\pm$1.36 g/dL; p = 0.235]. None of the differences were statistically significant. No thromboembolic complications were clinically detected

Table 3. Comparison parameters between control and TXA groups

	Control group	TXA group	Mean difference	95% CI	*p*-value
Hematocrit decreaseat 24 hours (%) mean ± SD	7.79±4.15	6.41±3.69	1.38±1.67	-2.11 to 4.87	0.419[□]
Hemoglobin decrease at 24 hours (g/dL) mean ± SD	2.51±1.36	1.79±1.39	0.71±0.59	-0.50 to 1.94	0.235[□]
Operative time (hours) mean ± SD	4.54±2.03	4.08±2.54	0.45±0.98	-1.59 to 2.50	0.649[□]
Intraoperative bleeding (mL) median (min-max)	600 (100 to 2,500)	300 (100 to 1,800)			0.356[□]
Volume of drained blood (mL) median (min-max)	100 (0 to 1,980)	180 (0 to 580)			0.740[□]
Blood transfusion (PRC units) median (min-max)	1 (0 to 15)	0 (0 to 5)			0.699[□]

[□] Independent t-test, mean±SD; [□] Mann-Whitney U test presented as median (min-max)

in either group (Table 3).

Discussion

Major operations on extremity primary malignant musculoskeletal tumors are associated with significant perioperative blood loss and a number of blood transfusions due to tumor-related factors, e.g., tumor characteristics, anatomic features of the surgical area (vascular proximity), major tissue trauma, duration of surgery, and intraoperative dilutional coagulopathy[15]. A mean total blood loss of 380 ml in wide resections has been reported by some authors[16]. There is a sharp increase in mortality rate related to transfusion-acquired infections and the immune modulation effects of allogenic blood; therefore, a reduction in blood transfusions would be beneficial. There are many modalities to reduce blood loss in major operations. TXA, an antifibrinolytic drug, is one of the pharmacological methods which is wildly used in knee, hip replacement, and spine surgery. Our hypothesis was that a prophylactic low dose of TXA in major surgical oncology of soft tissue and bone sarcoma in extremities could reduce blood loss and transfusion requirements.

Significant published data have reported that the administration of prophylactic TXA to patients undergoing major orthopedic procedures including total knee arthroplasty, total hip arthroplasty, and spinal surgery is effective in reducing perioperative blood loss and blood transfusion requirements[4-13]. A meta-analysis study reported variations in doses of TXA in orthopedic surgery. Twenty-one studies involved the administration of low-dose TXA (<15 mg/kg) and 18 studies involved the administration of high-dose TXA (15 mg/kg)[4]. Another study categorized the dose of TXA into 3 groups ≤1,000 mg, 2,000 mg, and ≥3,000 mg in patients undergoing total hip or knee arthroplasty in the United States[5]. Major operations on extremity primary malignant musculoskeletal tumors are associated with significant perioperative blood loss and a greater number of blood transfusions compared to other orthopedic procedures. In this study, we decided to use the maximum dose (3 grams) that has not been shown to induce venous thromboembolic events [VTE].

To the best of our knowledge, this is the first study of the efficacy of TXA for reducing blood loss in patients undergoing extremity primary musculoskeletal tumor surgery. The present study found clinical results similar to previous studies; however, differences between the control and study groups in this study were not statistically significant. That might be due to differences between the procedures used in musculoskeletal tumor surgery and those used in other types of orthopedic surgery. In this study, there were many uncontrollable variations in surgical method, e.g., the operative procedure used with each of the patients, operative time, and the individual patients' preoperative status. Although patients with musculoskeletal tumors are at risk of VTE, few detailed studies on the incidence or the clinical course of using TXA in these patients has been reported[15,17]. In this study none of the patients in either group had a thromboembolism event. The main strength of our study is the research design

and methodology, i.e., a randomized, double-blinded clinical trial of TXA in primary malignant musculoskeletal tumor surgery patients. The study does have limitations, however, namely the small sample size and variations in the type and size of the tumors. Additional controlled trials are needed to further evaluate the ability of TXA to reduce of blood loss in malignant musculoskeletal tumor surgery in greater detail. We suggest studies which include only one specific tumor type to further reduce variability.

Conclusion

The administration of TXA has a clinical effect in the decrease of intraoperative blood loss and transfusion requirements in patients undergoing extremity primary malignant musculoskeletal tumor surgery, but the effect is not statistically significant. No thromboembolic complications were clinically detected from the use of TXA.

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What is already known on this topic?

TXA is antifibrinolytic drug. The efficacy of tranexamic acid in reducing blood loss and blood transfusions in hip-knee replacement surgery, spine surgery, and surgical trauma cases in major orthopedic surgery without increasing the risk of thromboembolic events has been well documented.

What this study adds?

TXA has a clinical, but not statistically significant, effect in the decrease of intraoperative blood loss and transfusion requirements in patients undergoing extremity primary malignant musculoskeletal tumor surgery. TXA appears to cause no clinically detectable thromboembolic complications.

Potential conflicts of interest

The authors declare no conflicts of interest.

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