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Effects of Tranexamic Acid on Mortality and Blood Transfusion in Trauma Patients with Significant Hemorrhage: A Clinical Trial

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Abstract

Extensive hemorrhage is a significant cause of mortality in trauma patients. Tranexamic acid has been used for controlling bleeding in cardiovascular surgeries and dental manipulations in patients with hemophilia. However, in traumatic patients with bleeding, its use dates back to more recent years. This study aims to examine the effects of this drug on reducing mortality and blood transfusion rate in trauma patients with significant hemorrhage. A total of 60 patients with significant trauma-related hemorrhage (systolic blood pressure < 90 mmHg/heart rate > 110/min) from the emergency department of Imam Reza Hospital (Tabriz, Iran), were randomized in two groups. The case group received intravenous Tranexamic acid (1 g in 10 min and then 1 g over 8 h). The control group received placebo. Rate of transfusion and rate of one-month mortality were compared between the study groups. The mean ICU stay and overall hospitalization times did not have significant difference between two groups ($p<0.05$). Transfusion of packed cells was 6.03±1.50 and 6.03±1.22 units in case and control groups respectively. Transfusion of fresh frozen plasma (FFP) was 2.50±1.36 and 3.03±0.96 units in case and control groups respectively ($p=0.09$). Transfusion of platelets was 0.40±0.20 1.33±0.31 units in case and control groups respectively ($p=0.01$). Three patients (10%) in the case group and 4 patients (13.3%) in the control group were expired ($p=0.50$). Tranexamic acid is safe and effective in reducing platelet transfusion rate in patients with trauma-related significant hemorrhage. However, transfusion need and mortality would not reduce by its use in trauma patients.

Key Words: Trauma; Hemorrhagic shock; Tranexamic Acid; Transfusion

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Introduction

Trauma is the leading cause of mortality in 1-44 years-old population. Bleeding is a significant cause of death and complications in trauma patients (1). Hemostatic equilibrium is provided by processes of coagulation and fibrinolysis in traumatic patients (2). However, over-activation of fibrinolysis pathways could lead to uncontrolled hemorrhage and significant mortality (3). Hemorrhage control is achieved by surgical intervention, volume resuscitation and pharmaceutical therapies in traumatic patients. Anti-fibrinolytic agents have been successfully used to control bleeding in non-traumatic conditions. For instance, Aprotinin is an accepted drug for hemorrhage control in liver transplantation (4). However, use of anti-fibrinolytic agents in traumatic and trauma-related hemorrhagic shock is a novel strategy which could lessen mortality and morbidity (5, 6). A number of studies recommend that Tranexamic acid can be used safely in trauma patients to control hemorrhage and reduce mortality (7-10).

It is essential that traumatic bleeding is controlled in first ours of patients' admission (11, 12). Along with vital strategies of surgical interventions and volume resuscitation, anti-fibrinolytic agents could lessen the need for transfusion and reduce hemorrhage-related mortality (13-15). The effects of Tranexamic acid on reducing mortality in traumatic patients have been described by Shakur et al. and Morrison et al. in 2010 and 2012 respectively (16, 17).

The equilibrium of coagulation and fibrinolysis may compromise in traumatic shock and trauma-related hemorrhagic shock (18-20). Moreover, transfusion-related complications such as transfusion reactions, acute lung injury etc. could further complicate trauma patients receiving blood products (21-24). Thus, Tranexamic acid would reduce transfusion needs and may decrease morbidity and mortality in traumatic patients in hemorrhagic shock (25-27).

In the present study, we wanted to assess the effects of intravenous Tranexamic acid in reducing mortality and transfusion needs in trauma patients with significant hemorrhage. To our knowledge, this is the first study to investigate the effects of Tranexamic acid on bleeding control in Trauma patients in Iranian population.

Methods

In a randomized-controlled trial, we assessed the effects of Tranexamic acid on mortality and transfusion needs in traumatic patients with significant hemorrhage. The study was conducted at Imam Reza Hospital, Tabriz University of Medical Sciences, Tabriz, Iran. The study period was 16 months from January 2015 to April 2016. The entire patients were selected from Tabriz Imam Reza Hospital. This hospital is a level one trauma center and is the main and referral trauma hospital in East Azerbaijan province. During the study period, trauma patients were assessed for eligibility by our inclusion and exclusion criteria. Sixty patients were selected and were allocated to case and control groups. Each group contained 30 patients.

The inclusion criteria were patients between 15-50 years of age, systolic blood pressure (SBP) less than 90 mmHg or heart rate more than 110 per min or both, trauma to admission interval less than eight hours, and not being in need of emergent surgical intervention. The exclusion criteria were patients younger than 15 years of age, patients older than 50 years of age, having contraindication to receive Tranexamic acid (pregnancy, known thromboembolic events, defective color vision, history of vascular occlusive disease, hyper-coagulopathy, history of allergic reaction and history of angioedema), and being in need of emergent surgical intervention.

Study patients were divided into two groups of case and control groups. Randomization was conducted by www.randomizer.org. Figure 1 illustrates the follow diagram for randomized allocation of patients during the study. We administered Tranexamic to patients of case group within eight hours from trauma. Tranexamic acid was administered in 1 g dose (two 500 mg vials) infused by 100 ml of saline. Then, another 1 g dose was administered during eight hours. Tranexamic acid vials were products of Caspian Tamin Company (Tranexip 500 mg; 5 cc vials). For the patients in control group, placebo was administered. Placebo was consisted of 100 cc of saline and 10 cc of distilled water.

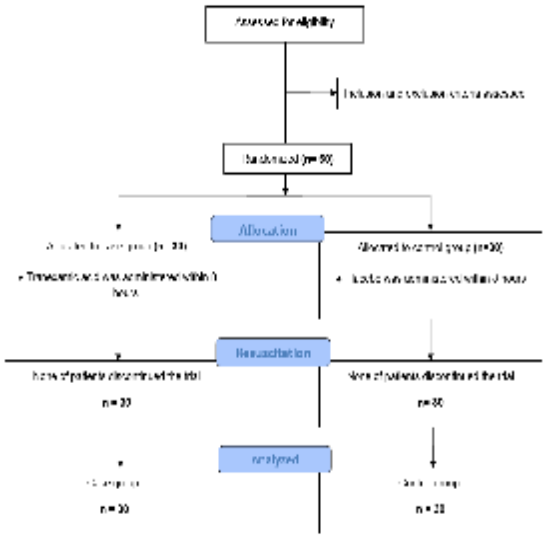

Figure 1: Follow diagram of study patients.

The outcomes of patients were assessed during hospital admission, discharge, and one-month after their admission. Duration of admission, intensive care unit (ICU) stay and mortalities were recorded and assessed in study patients. The extent of transfusion was adjusted by the rate of ongoing bleeding. After bleeding control, serum hemoglobin concentration of 10 g/dL, platelet count of 100'000 in 1 microliter of blood, and international normalized ratio (INR) of < 2 were target levels for cessation of administration of packed cells, platelets and FFP respectively. Normal saline was used as the only crystalloid fluid in all study patients. Albumin was also administered in patients with albumin level less than 3 g/dL. Bicarbonate solutions were also administered in patients with metabolic acidosis and arterial blood pH less than 7.1. Central venous pressure (CVP) was maintained 10-12 cm H_2O in all study patients in case and control groups.

Standard trauma care was conducted to all study patients in case and control groups based on Advanced Trauma Life Support (ATLS). All trauma procedures including ABC priorities, fluid therapy and resuscitation, intubation, fracture fixations, mechanical bleeding control and other essential strategies were conducted to all study patients. The only difference between case and control groups was administration of Tranexamic acid. Background variables were age, sex, time of trauma, type of trauma, and history of previous disease. Systolic blood pressure (SBP), pulse rate (PR), Glasgow coma scale (GCS), rate of administration of blood products (packed red cells, FFP and platelets), ICU admission, admission days, surgery and mortality were also recorded. All patients were visited and followed by chief-residents of surgery from admission to discharge and one-month after their admission. The patients were evaluated for complications of Tranexamic acid administration during the study.

The study was conducted in a double-blind research setting. The patients were unaware of their study group and were assessed by surgical residents and attending physicians by group numbers (group 1=case

group; group 2=control group). The investigators were also unaware of patients' intervention (Tranexamic acid or placebo). All data was collected by surgery residents and attending physicians and informed consent was obtained from patients. In the case of loss of consciousness or intubation, informed consent was obtained from patients' first degree relatives. All informed consents were obtained by surgery residents and attending physicians. The protocol of this study was accepted by research deputy of Faculty of Medicine and Vice Chancellor Office of Tabriz University of Medical Sciences, Tabriz, Iran. The study data were analyzed by SPSS 16.0 software. T-test, Fisher's exact probability test and chi-square test were used for analysis. P-values less than 0.05 were considered to be statistically significant.

Results

Thirty patients were assessed in each group of study. The intervention was administration of Tranexamic acid. Background variables were compared between two groups. These included age, sex, trauma type, interval from trauma to emergency department admission, pulse rate (PR), systolic blood pressure (SBP), GCS, and respiratory rate (RR). Outcomes were also assessed and compared between case and control groups. These included blood products administration (packed red cells, FFP and platelets), ICU administration, surgical ward administration, being in need for surgery and mortality. Table 1 illustrates background variables in case and control groups. There was not any significant difference between background characteristics of two study groups ($p > 0.05$).

Table 1: Background characteristics of patients in case and control groups

	Case group (Tranexamic acid)	Control group (Placebo)	p-value
Age[1]	37.6 ± 10.1	35.6 ± 10.5	p = 0.45
Sex[2]	23 males (76.7%)	22 males (73.3%)	p = 0.77
	7 females (23.3%)	8 females (26.7%)	
Trauma type[2]	Blunt: 29 patients (96.7%)	Blunt: 27 patients (90.0%)	p = 0.61
	Combined: 1 patient (3.3%)	Combined: 3 patient (10.0%)	
Time interval between trauma and admission[1]	4.3 ± 1.8 hours	4.1 ± 1.8 hours	p = 0.67
Pulse rate per minute[1]	121.3 ± 6.6	120.0 ± 5.1	p = 0.4
Systolic blood pressure	91.2 ± 1.5	89.5 ± 1.3	p = 0.21
GCS[1]	13.1 ± 2.3	14.0 ± 1.5	p = 0.21
Respiratory rate[1]	19.0 ± 2.5	19.2 ± 1.9	p = 0.68

GCS: Glasgow coma scale [1]Student's T test [2]Chi square [3]Fisher's exact probability test

Mean packed cell administration was 6.0 ± 1.5 and 6.0 ± 1.2 units in case and control groups respectively. T-test did not find any significant difference in packed cell administration in two study groups ($p = 0.99$). FFP administration was also 2.5 ± 1.4 and 3.0 ± 1.0 units in case and control groups respectively. The difference was not significant ($p = 0.09$). Platelet administration was 0.4 ± 0.2 and 1.3 ± 0.3 in case and control groups respectively. The difference in platelet administration was statistically significant ($p = 0.01$).

Mean admission in surgical ward was 6.6 ± 3.4 and 8.0 ± 4.8 days in case and control groups respectively. The difference was not significant ($p = 0.22$). Admission more than 28 days was seen in two patients in case group and in five patients in control group. Mean ICU admission was 4.6 ± 0.7 and 5.8 ± 0.8 days in two study groups respectively. The difference was not significant ($p = 0.26$).

Four patients (13.3%) necessitated surgery in case group while seven patients (23.3%) in control group underwent surgery. The difference was not significant (Chi-square; $p = 0.32$). All surgeries were orthopedic

operations in case group. Six surgeries were orthopedic and one surgery was thoracoscopic in control group.

The rate of mortality was 10.0% (three patients) and 13.3% (four patients) in case and control groups respectively. Fisher's exact probability test revealed the difference between mortality in case and control groups was not statistically significant ($p = 0.5$). Cause of death was brain injury in all three patients of case group (10%). Two patients (6.7%) of control group died because of bleeding. One patient (3.3%) died of brain injury and one patient (3.3%) died of multi organ failure (MOF) in control group. The difference between two group was not significant considering MOF, brain injury and bleeding ($p = 0.5$, $p = 0.61$ and $p = 0.49$ respectively).

Discussion

We assessed the effects of Tranexamic acid administration in reducing mortality and transfusion needs in patients with significant hemorrhage. The rates of mortality were 10% and 13.3% in case (Tranexamic acid) and control (placebo) groups respectively. The difference was not statistically significant. Transfusion needs were also compared between two groups. Only platelet administration was lower in patients receiving Tranexamic acid. The difference between packed red cells and FFP administrations were not significant.

The most clinically important research on the role of Tranexamic acid in trauma-related hemorrhage was CRASH-2 study in 2010. This study evaluated the effects of early Tranexamic acid administration (bolus of 1 g in 10 min and then infusion of 1 g in 8 hours) on 28-day mortality, vascular complications and transfusion needs in adult patients. CRASH-2 study assessed 20211 patients from 274 hospitals in 40 countries. The conclusion was lower mortality rate (14.5% in Tranexamic acid group vs. 16% in control group). However, complications and transfusion needs were not affected by Tranexamic acid administration (27). Our study also did not reveal any difference in packed cells and FFP infusions in patients receiving Tranexamic acid and placebo. However, CRASH-2 study shows a significant decrease in mortality. It should be emphasized that assessment of specific mortalities within case and control groups in CRASH-2 study illustrates that mortality only differs in hemorrhage-related deaths. Brain injury and MOF related mortalities were similar in case and control groups. In our study, we also did not find any difference between two groups of study in specific mortality rates.

Based on CRASH-2 study, in a comprehensive review, Ker et al. declare that using Tranxeamic acid in patients with trauma-related bleeding could decrease mortality and is recommended (28). A number of other studies also recommend use of Tranxemaic acid in trauma-related hemorrhage due to its potential effects in reducing mortality (6, 29). However, our study did not reveal any decrease in mortality. This may be in part due to our limited number of study sample.

Morrison et al. reviewed 896 files of trauma victims retrospectively. They revealed that mortality rate was lower in patients who received Tranexamic acid. Rate of coagulopathy episodes was also decreased in these patients. However, transfusion needs were not affected (17). Napolitano et al. also indicate that

Tranexamic acid could decrease mortality in trauma but it would not affect transfusion requirements (30). Our study showed a decrease in platelet use in Tranexamic acid group.

Although the literature review reveals lower mortality in trauma patients receiving Tranexamic acid (27-30), transfusion requirements are not affected significantly. This is a matter of controversial issue to understand the underlying mechanism which could decrease mortality rate. Tranexamic acid is an anti-fibrinolytic agent that inhibits plasmin. Plasmin is a pro-inflammatory agent which could activate monocytes, neutrophils and endothelial cells. Thus, regulation of inflammatory mechanisms by Tranxemaic acid may play a more important role in reducing mortality (31-37).

Our study did not show that Tranexamic acid could decrease mortality in patients with trauma-related hemorrhage. However, literature review illustrates that Tranexamic acid is of potential use and clinical interest in trauma bleedings. A number of other studies propose that patients' conditions should be assessed prior to administration of Tranexamic acid in trauma-related hemorrhages. Thromboelastography is a method of evaluation prior to Tranexamic acid use (38-43).

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Conflicts of interest

NONE

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