Original Article

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The New Age of Trauma Resuscitation – Introducing Tranexamic Acid in an Accident & Emergency Department in Karachi Pakistan

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Abstract

Background: In traumatic patients there is increase loss of blood and requires excessive blood transfusion as compared to other diseases. Clinical efficacy and clinical safety of tranexamic acid in decreasing blood loss assess during this study in post traumatic patients.

Method: Prospectively conducted randomized doubleblind placebo controlled study carried out. Patients were blindly randomized into two groups to receive either intravenous 1gm tranexamic acid 20 min or similar volume of 0.9% saline as placebo (P).Inclusion criteria was based on pulse rate >110 per min or systolic pressure level <90mmHg, hemorrhage or in danger of serious hemorrhage. Patients' total blood loss was measured, needs of transfusion and hospital stay recorded. The post traumatic hemoglobin, hematocrit values, serum creatinine, activated thromboplastin time, prothombin time, platelets count and pulmonary embolism symptoms were comparatively evaluated.

Results: The total measured blood loss in tranexamic acid group (276 ± 53 mL) when comparing to control group (523 ± 74 mL) was less significantly. The requirement of blood transfusion in comparison was high in the control group and post traumatic hematocrit values were higher with in the tranexamic acid group.After administration of tranexamic acid in traumatic patients there have been no clinically relevant differences within the vital signs and no thromboembolic complications were detected in either group.Conclusion: In traumatic patients, the prophylactic usage of tranexamic acid has effectively decreased blood loss, transfusion needs and hospital stay without any complication or adverse effects of thrombosis. Thus, TXA can be used safely and effectively in trauma subjects.

Keywords: trauma, tranexamic acid, blood loss, transfusion, hospital stay.

Introduction

Tranexamic acid (TXA) is a amino acid lysine synthetic derivative. Upon stimulation of plasminogen to the serine protease causes competitive inhibition of plasmin, thorough binds with kringle domains by TXA. Impairment of fibrinolysis occurs by blocking plasminogen lysine binding sites that cause inhibition of plasminogen stimulation and causes inhibition of fibrin binding to plasminogen[1]. Tranexamic acid plasma half life is 2 hours and TXA distributed throughout all body tissues1. Breakdown/fibrinolysis of blood clot is a physiological response to trauma & surgical procedure so as to continue vascular capability and in some cases it becomes exaggerated hyperfibrinolysis. Antifribrinolytic medications can decrease blood loss by preventing clot breakdown [2]. Side effects are uncommon and include gastrointestinal effects, headache, fatigue, dizziness, and hypersensitivity reactions[3]. TXA as a potent substance to inhibition of fibrinolysis was initially reported by Okamoto in 1962[4].It has been in use for many years for reducing the blood loss in surgeries like, transurethral prostatic surgery, urinary tract surgery, cardiothoracic bypass surgeries, orthopedics arthroplasty or orthotopic liver transplantation[5] and in patients with traumatic hyphema it reduce the rates of re-bleeding[5]. TXA found to be very useful in trauma patients in decreasing blood loss and decrease rate of transfusion of blood. There is a paucity of local data as no study to date has been conducted in the emergency room of hospitals in Karachi, Pakistan on TXA efficacy in reducing blood loss. The greatest trial of antifibrinolytics up to now is that the Clinical Randomization of Antifibrinolytics in Significant Haemorrhage (CRASH-2) trial, that assessed the consequences of initial administration of tranexamic acid (TXA) in traumatic patients with hemorrhage or in danger of considerable hemorrhage (CRASH-2 trial). All cause mortality was considerably decreased with TXA[6]. The excitement concerning applying the findings of CRASH-2 is that, the global problem is a death due to traumatic bleeding, and everyone those with trauma or at danger of traumatic hemorrhage, this might lead to a reduction within the range of deaths of 120 000 per year worldwide if TXA was given to them 6. Reduce deaths in a trauma patients of large population have recently been shown by usage TXA 6. As a result, around the world TXA is currently being introduced into trauma protocols[7, 8, 9]. TXA has been incorporated in the World Health Organization list of mandatory medicines[10] on the premise of the CRASH-2 trial results. The Meta analysis published by Ker et al[11] additionally recommended that a dose of 1 gram produced a reduction in hemorrhage that by adding higher doses was not improved. This study found that for most adults a complete dose of one gram was likely to be adequate and there was no

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proof to support additional doses of TXA. Since 2010, there are variety of articles with additional dose of TXA describing seizures; using doses a lot of higher than original Horrow recommendations[11,12]. Though ultimately limiting the dose of TXA to the initial dose recommended by Horrow seems as safe and effective as additional dose. Exsanguination (hemorrhage) is responsible for 40% of preventable trauma deaths[13]. Besides in traumatic patient, haemorrhage being directly liable for mortality in most of the early in-hospital patients, haemorrhage may also contribute to late mortality associated with failure of multiple organs 13. Hemorrhage in trauma patients might create complex and distinctive coagulopathy; where multiple mechanistic factors like consumption of factors, coagulation factor dilutions, hypothermia, acidosis, excessive clot breakdown (hyperfibrinolysis) and poor fibrinogen utilization are responsible for its development[14] In this study, the aim was to see the safety and effectiveness of TXA in trauma patient in decreasing the loss of blood in a tertiary care hospital in Karachi Pakistan.

Methods

Prospectively conducted randomized double blinded placebo controlled study started from Dec 2016 and completed in April 2017 in Accident and Emergency Department of Jinnah Postgraduate Medical Center. 500 consented patients, with informed consent who met the inclusion criteria, blindly randomization done into 2 groups to be given either intravenous 1 gm tranexamic acid over 20 min or an equivalent volume of distilled water as placebo (P). Randomization simply done by collecting randomly the blurred paper bags which contains either placebo ampoules or contains one gram TXA. Analyzation of these envelopes was at the time of result analysis to overcome the bias. Preparation of TXA injection was done by diluting one gram (10 mL) TXA in 20 ml of 5% dextrose water. While dilution of sterile water also done with 20 ml of 5% dextrose water for intravenous (IV) injection (placebo). Inclusion criteria included: pulse rate >110 per min or systolic pressure level <90mmHg, hemorrhage or in danger of serious hemorrhage. Exclusion criterion includes: allergic to TXA, anemia, hepatorenal dysfunctions, known serious cardiothoracic diseases, coagulopathies or any history of thromboembolic disease/ deep vein thrombosis. The heart rate, ECG, arterial blood pressure and peripheral pulse oximetry were observed in continues fashion. Due to hemorrhage if patients had signs of hemodynamic instability despite adequate volume replacement (heart rate more than 120 per min or a decrease in systolic BP level by more than 20% of base value), blood transfusion was given. Quantity of blood losses were calculated by weighing soaked surgical swabs, operation drapes, sponges and calculating the blood volumes in the suction drain bottles. All patients' total blood loss was measured and recorded at the 12 hour post trauma period. We also recorded the patients' need of transfusion and their hospital stay. The post traumatic hemoglobin, hematocrit values, serum creatinine, activated thromboplastin time, prothrombin time, platelets count and manifestation of thromboembolism and pulmonary embolism such as dyspnea, pleuritic chest pain, apprehension, tachypnea, tachycardia, rales etc. were comparatively evaluated. P value of <0.05 was considered statistically significant. Statistics was scrutinized by SPSS 21.

Table-1: Demographic profile, hemoglobin and coagulation parameters

Parameters	Group P	Group TXA	
Age (years)	46.3 ± 18.2	47.9 ± 13.1	(P value <0.01)
Hemoglobin (gm·dL)	09.8 ± 1.3	10.6 ± 1.5	(P value <0.01)
Hematocrit (%)	29.36 ± 1.8	30.14 ± 2.2	(P value <0.01)
Platelet count (x10 u/L)	264.46 ± 34	273.42 ± 35	(P value <0.01)
Prothrombin time (sec)	13.9 ± 0.8	14.1 ± 2.1	(P value <0.01)
aPTT (sec)	34.9 ± 4.9	32.9 ± 3.7	(P value <0.01)

Table-2: Comparative values of measured blood loss, blood transfusions and hospital stay.

Parameters	Group P	Group TXA	
Measured blood loss (mL)	523 ± 74	276 ± 53	(P value <0.01)
Blood transfusions (n)	115	70	(P value <0.01)
Hospital stay	7 ± 3	5± 2	(P value <0.01)

Results

In demographic data there was no significant distinction between both groups. (table-1). The total measured blood loss (276 ± 53 mL) in TXA group was considerably less when comparing with control group (523 ± 74 mL) (P<0.01). In the control group the need for blood transfusion was more, transfusion (n) 115 in placebo group as compared to 70 in tranexamic acid group. Decrease hospital stay was noted in tranexamic acid group 7 ± 3 in placebo group as compared to 5± 2 in TXA group (table-2). Post traumatic hematocrit values were high in the TXA group while coagulation profiles have no difference between both the groups. After administration of tranexamic acid in traumatic patients there have been no clinically relevant differences within the vital signs and no thromboembolic complications were detected in either group during hospitalization.

Discussion

This study has evaluated the safety and efficacy of tranexamic acid in the emergency unit to decrease the loss of blood during trauma resuscitation. Hemostasis rests upon a balance between the coagulation, fibrinolytic and complement pathways, with a series of complex interactions between platelets, plasma proteins, viscosity and blood flow, and the endothelium. Perivascular, tissue factor-expressing cells are exposed to blood by an injury to the arterial or venous wall leading to the coagulation cascade[15]. Blood transfusions are associated with the risk of anaphylaxis, hemolytic reaction, acute lung injury and infection transmission. Blood transfusions carry the potential of adverse immune consequences and end organ effects. Moreover, it is a potentially expensive and scarce resource. The prophylactic administration of tranexamic acid has shown a significant decrease in total measured blood loss and has reduced the need of blood transfusions in this study.

The risk of death from hemorrhage and a reduction in the risk of arterial thrombotic event are both possibly achieved by administration of Tranexamic acid. This may be possible by tranexamic acid's role in reducing myocardial oxygen demand and increasing the supply by limiting bleeding. Moreover, the reduction in the arterial thrombotic events could be attributed to an anti-inflammatory effect of tranexamic acid[16,17]. Our data confirmed that there is decrease in blood loss in tranexamic acid treated patients. The CRASH-2 RCT reported a decrease in deaths due to bleeding in the TXA group as compared to the placebo with RR of 0.68[18]. TXA does not induce platelet

activation, and our results were consistent with this fact. The platelet count in our study was similar in both groups. The extrinsic coagulation (PT) and the intrinsic pathway of coagulation (aPTT) in both groups was not affected by the administration of tranexamic acid and were noted to be within their reference range in both groups. Weber, C. F., et al. studied the effect of TXA on platelet function on patients who were on dual antiplatelet therapy and concluded that TXA actually reverses platelet aggregation dysfunction due to antiplatelet medication[19]. This would be a significant advantage in trauma victims who were taking antiplatelet therapy. However, whether our trauma patients were on antiplatelet therapy was out of the scope of our study. A rapid intravenous administration of TXA may cause hypotension and therefore it is recommended to be given as a slow infusion. In our study, no case of thromboembolism was reported with TXA while with tranexamic acid the incidence of venous thromboembolic events was 0.7%, with aprotinin 1.4% and with placebo 1.5% in a recent review [20]. The use of TXA is particularly advantageous in countries where blood is readily available; because fewer units of blood will be transfused. This decreases the risk of transfusion-transmitted viral infections. Our study shows significant decrease in the bleeding volume in the TXA group as compared with the placebo group. Current data concludes that the administration of TXA to patients with traumatic bleeding, within three hours of injury, significantly reduces mortality with no apparent increase in adverse thrombotic events[18]. However, in Pakistan, no previous study was conducted to record the use of TXA in trauma victims. Each year, injuries claim lives of 5 million people worldwide. Two of the three top causes of injury related deaths; road traffic accidents (24%) and falls (14%) are predicted to rise as compared to other causes of death. Globally, road traffic accidents are the leading cause of death in the 15 – 29 year age group and they are estimated to become the 7th leading cause of death by the year 2030[21]. Data shows that 85% of road traffic deaths occur in the lower-middle income countries (LMIC)[22]. Pakistan and other lower-middle income countries (LMIC) where injuries are the leading cause of death in the young population age can potentially benefit from the use of TXA in trauma victims during resuscitation. Pakistan has an underdeveloped pre-hospital trauma management system and casualties are brought to the major public accident and emergency centers via untrained paramedics and unequipped ambulances. Violence and terrorism related injuries are often brought to the hospital via 'scoop and run' by charity run ambulances which are unequipped patient transport vehicles[23]. Analysis from injuries sustained by policemen in an improvised explosive device bombing and three separate episodes of bombing in the city of Karachi show that most victims were brought within the golden hour to the emergency unit of our study center [24]. This makes many of our trauma victims eligible for TXA treatment especially due to the lack of resuscitation or hemorrhage control during transport. Another study at a private tertiary hospital in Karachi however calculates the mean time from the occurrence of injury to reaching the ER as 4.7 hours with only 30.0% of victims reaching within the golden hour [25]. This further underlines the importance of using TXA at public sector hospitals as they receive the bulk of trauma victims and are involved in referring and transferring patients to private hospitals. The CRASH-2 trial calculates the OR of tranexamic acid on death from hemorrhage when administered immediately after injury at 0.61. The OR is multiplied by 1.15 for each hour that passes by from the time injury[18]. This further highlights the critical time of intervention for maximum reduction in mortality. The resuscitation of trauma victims at the risk for hemorrhage and traumatic coagulopathy should include TXA before referral to other centers. Recommendation on the usage of TXA in the management of trauma victims.

1. Trauma patients with evidence of bleeding should be routinely administered Tranexamic acid.
2. Transfusion protocols for trauma should include Tranexamic Acid.
3. The administration of Tranexamic acid should be within 3 hours form the onset of injury/
4. The dosage administered should be 1g of TXA intravenously (as a bolus over 10 minutes) which is followed by an infusion of 1g over 8 hours.

Conclusion

In traumatic patients, the prophylactic usage of tranexamic acid has statically significant in decreasing blood loss, transfusion needs and hospital stay without any complication or adverse effects of thrombosis. Thus, TXA can be used safely and effectively in trauma subjects.

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