
بسم الله الرحمن الرحيم

Effect of oral tranexamic acid on prevention of rebleeding in patients with acute uepper gastrointestinal bleeding

Naghme Habibi

Internal Medicine Resident

Ahvaz Jondishapur University of Medical Sciences

INTRODUCTION

Upper gastrointestinal bleeding (GIB) is a common cause of admissions at hospital emergency departments and a common complication among in hospitalized patients .

The mortality and morbidity rates in the patients who experience rebleeding are 20%. In the patients referred to endoscopy for suspected upper GIB, 30-day mortality rate is 10- 14% .

In recent years, various methods, including drug therapy, sclerotherapy, and surgical procedures have been used to treat GIB . Endoscopic interventions have an important role in reducing mortality in GIB patients .

Endoscopy is an effective method for reaching therapeutic and diagnostic goals in the treatment of both upper and lower GIB . Many medications can reduce the risk of rebleeding and the need for reduction of mortality surgery or blood transfusions.

However, mortality rates for recovery in patients with upper GIB are very different . Generally, there are no effective drugs to prevent bleeding from gastric and duodenal ulcers . Fibrinolysis may play an important role in bleeding.

It may also increase the risk of rebleeding . Tranexamic acid (TXA) is an anti-fibrinolytic agent that reduces fibrinolysis by slowing the conversion of plasminogen to plasmin .

The formation of TXA-plasminogen prevents the degradation of fibrin networks . According to a comprehensive clinical trial, TXA reduces mortality in trauma bleeding patients by 9% .

In the present study, we sought to investigate the role of prescribing oral TXA in early hours in improving the consequences of acute GIB, the need for re-endoscopy, reduction of endoscopic and surgical interventions, and

PATIENTS AND METHODS

Study population

Participants in this clinical trial included 375 patients with suspected upper GIB whos condition was confirmed either by endoscopy or through clinical manifestations such as gastric lavage, hematemesis, or melena, who referred to the Imam Khomeini Hospital (Ahvaz, Iran) from September 2018 to July 2019.

Exclusion criteria were history of gastric cancers and presence of contraindication or history of sensitivity to TXA.

Study design

Participants were randomly assigned to one of three treatment groups: Group A, oral TXA 1000 mg daily for three days; Group B, TXA 500 mg capsule daily for three days (TXA capsule containing 250 mg); Group C, control group receiving no oral TXA and treated with placebo under similar conditions.

In this three-blind trial, none of the patients studied, the researchers, and the data analyzers were aware of the control and test groups. All patients in the emergency department received routine and conventional treatment (intravenous fluids and proton pump inhibitors).

Information about the period from admission until the first required endoscopy, the need for endoscopic intervention and the type of intervention, the extent of the lesion found and its type, requiring blood transfusion, the occurrence of gastrointestinal rebleeding, the need for intervention surgery and

radiology, drug complications, the number of days in the intensive care unit (ICU), and death was recorded.

Afterwards, all of the above events were reviewed within 72 hours. The blood transfusion requirement for most patients was defined as Hb <7 g/dl (70 g/l) and was aimed at maintaining a level of ≥ 7 g/dl (70 g/l). The threshold may be higher at Hb ≥ 9 g/dl (90 g/l), in high risk patients with significant side effects in the setting of significant anemia .

Rebleeding was defined as obvious hematemesis; fresh blood passes through the rectum; a decrease in Hb level of >2 g/l at any 24h after first day following endoscopic homoeostasis; the presence of bright blood in the stomach or duodenum, or both, is more frequent at endoscopy when there is suspicion of more bleeding; or shock in the constant presence of melena.

Statistical Analysis

Data were analyzed by SPSS version 20. For descriptive analysis of qualitative data, frequency and relative frequency were used.

ANOVA and chi-square tests were used to compare the means of the groups. For multivariate comparisons, regression analysis and logistic regression were used. P values less than 0.05 were considered statistically significant.

RESULTS

Patients' Characteristics:

The study included 375 patients, 76.5% of whom were male 98 and 23.5% were female. Their age ranged from 22 to 89 years (mean 13.49 ± 56.3). There was no significant difference between the three groups in terms of sex (P = 0.26) and age (P = 0.5). The patient data are presented in Table 1.

Of all participants, 108 had no past medical history (41 in the placebo group, 39 in the TXA 500 mg group, and 28 in the TXA 1000 mg group), but this variable included diabetes mellitus (12%), hypertension (HTN) (12.8%), ischemic heart diseases (IHD) (10.4%), renal disorders (RD) (2.66%), simultaneously DM and HTN (17.86) coexistence of DM and HTN and IHD (8.8%), coexistence of HTN and IHD (1.33%), simultaneously DM and HTN and IHD and RD (0.8%), and cirrhosis (4.26%) in other patients.

The frequency of HTN and DM was higher than that of other underlying diseases (23 patients in the placebo group, 19 in the TXA 500 mg group, and 25 in the TXA 1000 mg group).

- Of all patients, 51 patients did not provide information about their medication history, and of the remaining 324 patients, 170 were taking aspirin (60 in the placebo group, 53 in the 500 mg group, and 57 in the 1000 mg group) and 82 patients had a history of analgesic use (26 in the placebo group, 32 in the 500 mg group, 24 patients in the 1000 mg group) were the most frequently used medications.

Comparison of clinical findings between groups

Flat pigmented was the most common ulcer type (46.4%) of GIB overall. The frequency of the other types of ulcer was as follows: 24% visible vessel, 17% oozing ulcer, 8% adherent clot and 8% esophageal varices. No significant differences were seen in the three groups according to the ulcer types (P = 0.93) (Table 2).

RBC packed cell (PC) transfusion was 44% in the placebo group, 38% in the TXA 500 mg group, and 28% in the TXA 1000 mg group, with the lowest percentage receiving P.C units, with a significant difference in the 1000 mg group (P <0.0001) (Table 3).

Rebleeding occurred in 45 patients, including 13 in the placebo group (10.3%), 10 (8%) in the TXA 500 mg group, and 12 (9%) in the TXA 1000 mg group. In the TXA 500 mg group, bleeding was significantly lower (P <0.0001). The highest bleeding occurred on Day 2 (23 out of 45 with rebleeding) (Table 3).

TABLE 2. Comparison of variables between groups, before intervention.

Variable	Mean ± SD or n (%)			P-value
	1000 mg TXA (n= 125)	500 mg TXA (n= 125)	Placebo (n= 125)	
Sex (male/female)	99 (79)/ 26 (21)	100 (80)/ 25 (20)	88 (71)/ 37 (29)	0.26
Age (y)	56 ± 12	54 ± 13	56 ± 14	0.5
Clinical findings				
Systolic blood pressure (mmHg)	87.28 ± 51.74	85.28 ± 50.6	108.24 ± 23.72	0.0002
Diastolic blood pressure (mmHg)	75.6 ± 5.44	72.32 ± 5.97	73.56 ± 7.31	< 0.0001
Temperature (°C)	37.1 ± 0.1	37.14 ± 0.11	37.12 ± 0.1	0.51
Pulse rate (/min)	82.87 ± 3.43	83.91 ± 5.21	83.08 ± 3.28	< 0.0001
Ulcer type				
Flat pigmented	62 (49%)	54 (43%)	58 (46%)	
Adherent clot	0	3 (2%)	5 (4%)	
Visible vessel	25 (20%)	38 (30%)	28 (22%)	0.93
Varices (F2-F3)	8 (6%)	13 (10%)	11 (8%)	
Oozing ulcer	29 (23%)	16 (12%)	22 (17%)	
Angio dysplasia	1 (0%)	1 (0%)	1 (0%)	
Laboratory findings				
Initial Hb (g/dl)	10.09 ± 2.33	9.13 ± 3.62	9.63 ± 2.65	0.037
Prothrombin time (INR)	1.1 ± 0.11	1.12 ± 0.15	1.14 ± 0.13	0.86
Creatinine (mg/dl)	1.06 ± 0.59	1.02 ± 0.6	1.02 ± 0.27	< 0.0001

Hb, Hemoglobin; TXA, Tranexamic acid.

ICU admission was 23% (n = 28) in the placebo group, 18% (129 n = 25) in the TXA 500 mg group, and 13% (n = 16) in the TXA 1000 mg group, indicating that the need for ICU admission in the TXA 1000 mg group was significantly lower (P = 0.008).

Overall, 69 patients required ICU admission, with 54 requiring one day and 15 requiring more than one-day admission (Table 3).

The mean time period from admission to endoscopy in the three groups was compared using ANOVA with a p-value of 0.58 showing no significant difference among the three groups (An average of seven hours in all three groups) (Table 3). No deaths, radiological interventions or surgical interventions were recorded among all three groups of patients .

TABLE 3. Comparison of variables between groups, after intervention.

Variable	Mean ± SD or n (%)			P-value
	1000 mg TXA (n= 125)	500 mg TXA (n= 125)	Placebo (n= 125)	
Patients hospitalized in ICU (n)				0.008
No hospitalization	109 (87)	100 (80)	97 (77)	
One day	14 (12)	23 (19)	17 (14)	
Two day and more	2 (1)	2 (1)	11 (9)	
Endoscopy intervention (n)				0.71
No intervention	63 (50)	58 (46)	60 (48)	
APC or Hemoclip	53 (42)	54 (43)	54 (43)	
Ligation band	9 (7)	11 (8)	7 (5)	
Salin injection	0	2 (1)	4 (3)	
Total intervention	62 (49.6)	67 (53.6)	65 (52)	
Rebleeding (n)				< 0.0001
No rebleeding	113 (91)	115 (92)	112 (89.7)	
First day	0	0	4 (3.8)	
Second day	8 (6)	8 (6.7)	7 (5.2)	
Third day	4 (3)	2 (1.3)	2 (1.3)	
Patients received RBC PC (n)				< 0.0001
No receive	89 (72)	77 (62)	71 (56)	
One unit	4 (3)	2 (1)	19 (16)	
Two unit	27 (21)	32 (26)	28 (23)	

Comparison of laboratory findings between groups

Analysis of variance was used to compare temperature, heart rate, international normalized ratio (INR), creatinine, initial hemoglobin and post-transfusion hemoglobin and creatinine ($P < 0.0001$). Temperature ($P = 0.51$) and INR ($P = 0.86$) were not significantly different among groups (Table 2).

DISCUSSION

Endoscopic treatments by injection or heater probe can reduce rebleeding and the need for surgery in clinical trials.

Success in these procedures depends on the skill of the operator, and they may not be effective under conditions other than the testing conditions . Therefore, any drug treatment that is easily administered and improves upper GIB is an important step forward .

In this study, we investigated the effect of TXA on upper GIB. The clinical justification for the use of TXA is evidence showing that TXA is successful in controlling different tissue bleeding, modifying homeostasis, and stopping severe GI bleeding.

- TXA inhibits plasminogen, a major enzyme involved in fibrinolysis, and directly decreases pepsin fibrinolytic activity. It has recently been shown that TXA has anti-inflammatory effects (23). However, the role of oral TXA as a treatment for upper GIB is not well understood.

- The recommended dosage for TXA is 0.5–1 g (10– 15 mg/kg), delivered intravenously 3–4 times per day (24). Therefore, in this article we used doses of 500 and 1000 mg.

In our study, the rate of rebleeding was significantly lower in the group receiving TXA 500 mg, which is similar to results reported in one meta-analysis study where TXA was found to reduce bleeding significantly.

In another study on dialysis patients with upper GIB, the rate of rebleeding was significantly reduced.transfusion rate was lower in case group but this difference was not significant.

Another study reported that TXA 2 g followed by 1 g reduced blood amount in endoscopic evaluations but had no significant effect on rebleeding in upper GIB.

However, in that study, the number of patients was insufficient to detect the effect of intervention on clinical findings .

Therefore, further studies are needed to confirm the effect of different dose of TXA on reducing rebleeding. According to the findings of the present study, the frequency of RBC PC transfusion was significantly lower in the TXA 1000 mg group. Sabovic et al's study showed that the rate of blood transfusions in the upper GIB group receiving TXA 20 mg intravenously decreased significantly .

Therefore, TXA intake is associated with a decrease in transfusion rate in upper GIB. Overall, in our study, TXA intake was associated with a significant decrease in rebleeding and the rate of blood transfusion.

The therapeutic and diagnostic role of endoscopy is crucial in the management of GIB unless these conditions require immediate intervention .

In this study, the need for endoscopic intervention (Despite a decrease in TXA 1000 mg group) and endoscopy time was not significant different between the groups. Also, Tavakoli et al report that the endoscopic and/or surgical intervention rates and endoscopy time were not statistically different in the TXA groups compare with placebo .

The most common gastrointestinal side effects associated with TXA administration are diarrhea and nausea .

In this study, we used oral TXA and did not observe any side effects. Also, length of stay at ICU was significantly shorter in the TXA 1000 mg group (P= 0.008), and the need for two or more days in ICU was similar in both 200 500 and TXA 1000 mg recipients and was less than that in the placebo group. There were no deaths in the study.

In one meta-analysis study, both the rate of death and the need for emergency surgery significantly reduced in upper GIB patients receiving TXA (25). Therefore, TXA intake was a safe treatment with no associated significant complications.

Consequently, with respect to the rate of rebleeding and mortality, absence of any significant side effects, the relative safety of this treatment, and low cost of the drug, our study confirms the positive effect of TXA on upper GIB control. Given the unicentrality of the present study, further multicentral studies are needed.

Thank You for Your Attention