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Effect of tranexamic acid on the treatment of patients with upper gastrointestinal bleeding: A double-blinded randomized controlled clinical trial

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ABSTRACT

Objective: To determine the efficacy of tranexamic acid (TXA) in the management of acute upper gastrointestinal (GI) bleeding.

Methods: A total of 70 patients with acute upper GI bleeding were included in this double-blinded randomized controlled clinical trial from September 2018 to December 2018. Patients were divided into the control group (received fluid therapy and intravenous infusion of pantoprazole, 35 cases) and the TXA group (received intravenous TXA besides the treatment of control group, 35 cases). Rebleeding, admission duration, and need for blood transfusion were compared between the two groups.

Results: Fifteen patients (42.9%) in the TXA group and 10 patients (28.6%) in the control group stayed in hospital for more than 3 days during their admission (P=0.21). Rebleeding occurred in 8 patients (22.9%) and 5 patients (14.3%) of the TXA group and the control group, respectively (P=0.35). More patients in the TXA group (21 cases, 60%) received blood transfusion than the control group (8 cases, 22.9%) (P=0.02).

Conclusions: TXA did not improve the outcome of patients with acute upper GI bleeding.

KEYWORDS: Tranexamic acid; Gastrointestinal bleeding; Emergent; Treatment

1. Introduction

The gastrointestinal (GI) system is divided into upper GI and lower GI tracts. The upper GI tract begins from the mouth and continues through the second part of the duodenum (the ligament of Treitz). Acute GI bleeding is one of the most common medical emergencies and is one of the most common causes of mortality and morbidity worldwide[1]. GI bleeding could be obvious or occult. Obvious GI hemorrhage can be seen in disorders such as hematemesis, melena, and hematochezia. Acute upper GI bleeding has a higher prevalence than lower tract GI bleeding by 4 to 5 times[2]. The most common causes of acute upper GI bleeding in developed countries are peptic ulcers and esophageal varices[3,4]. A major predictor of death in GI bleeding is rebleeding, occurring in 10% of non-variceal bleeding patients[5].

Endoscopic procedures along with pharmacologic therapies are used for the management of acute upper GI bleeding. Pharmacologic agents used in such patients include proton-pump inhibitor agents, H_2-blockers, somatostatin analogues, and tranexamic acid (TXA)[6]. TXA is a synthetic lysine analogue, which is bound to plasminogen and plasmin and blocks their ability to bind the remaining lysine in fibrin, and therefore prevents fibrinolysis[7]. TXA can reduce upper GI bleeding and help to stabilize the patients' condition before endoscopic treatments[8]. The evidence regarding the TXA effect indicates its efficacy in decreasing hemorrhage during operations and bleeding due to traumatic injuries. TXA is prohibited in patients with previous allergic reactions to TXA, renal failure, active hematuria, and neurologic disturbances including seizures[9]. TXA can also decrease the mortality of GI bleeding patients[10]. With this background in mind, we decided to determine the efficacy of TXA in patients with acute upper GI bleeding.

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2. Patients and methods

2.1. Study participants

This was a double-blinded, randomized clinical trial. The study was carried out in patients with the diagnosis of upper GI bleeding referred to the emergency department at Imam Reza Hospital, Kermanshah, Iran from September 2018 to December 2018. We excluded patients with age <18 years, contraindications to receiving TXA, kidney disorders, pregnant or lactating women, esophageal or gastric varices, coagulation disorders, and severe liver disease. To establish the diagnosis of upper GI bleeding, all patients underwent endoscopy during the first 24 hours of admission. In case of other diagnoses during endoscopy except for upper GI bleeding, the patient was excluded.

2.2. Ethical approval

Informed consent was obtained from the patients. This study was performed in accordance with the tenets of the Declaration of Helsinki. The study was approved by the Ethics Committee of the Kermanshah University of Medical Sciences (approval number: IR.KUMS.REC.1397.97101). The study was registered at the Iranian Registry of Clinical Trials (www.irct.ir) as IRCT20130812014333N92.

2.3. Sample size

Considering confidence of 95% and power of 90%, the sample size was calculated (using the following formula) as 29 patients in each group[11]. Based on this sample size, 35 patients were included in each group.

$$N=\frac{(Z_{1-\alpha/2}+Z_{1-\beta})^2(\sigma_1^2+\sigma_2^2)}{(\mu_1-\mu_2)^2}=\frac{(1.96+1.28)^2(1.3^2+1.5^2)}{(2.6-1.4)^2}=29$$

μ_1: The first population mean; μ_2: The second population mean; σ: Standard deviation; α: Type Ⅰ error; Type Ⅱ error; Z: Confidence level; $1-\beta$: Power; σ_1^2: First population variance; σ_2^2: Second population variance; N: Sample size.

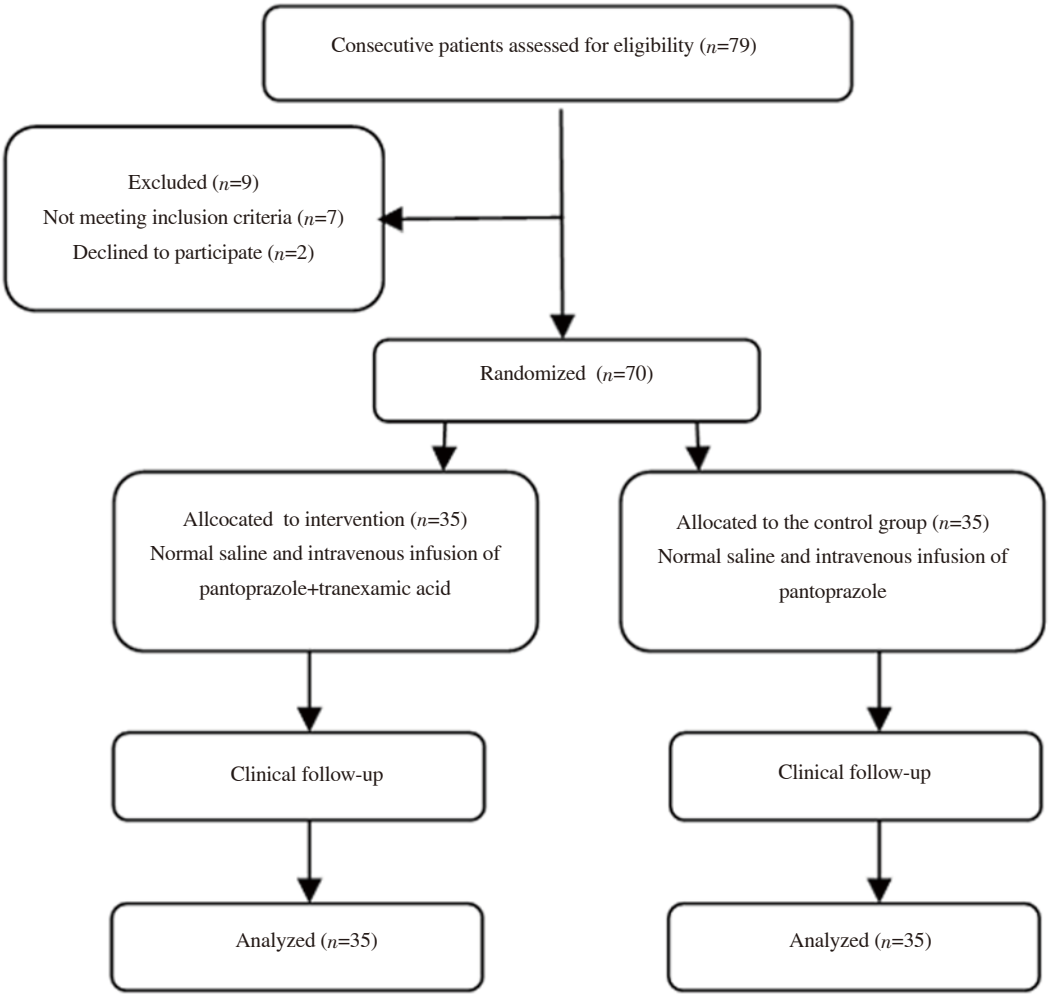

Figure 1. Flowchart of the allocation, follow-up and analysis of this clinical trial.

2.4. Study design

The patients were randomly divided into two groups by emergency department nursing staff who were blinded to the study. The control group received conventional treatments for upper GI bleeding including fluid therapy and pantoprazole infusion. In the TXA group, besides conventional treatments, TXA was injected stat and then intravenous infusion of TXA (1 g/8 h) was administered. Individual information was gathered from medical records and clinical examinations of the patients during admission. The outcomes of the study were hospital length of stay, the need for endoscopy and blood transfusion, and rebleeding. The patients were followed up for 1 month.

2.5. Statistical analysis

All statistical analyses were conducted using the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean±standard deviation (SD), and descriptive data were expressed as frequency and percentage. The Kolmogorov-Smirnov test was performed to evaluate the normal distribution of the data in each group. Independent-samples Student's *t*-test was used to assess the between-group comparisons. Categorical variables were compared using the *Chi*-square test. The significant level of this study was set at α=0.05.

3. Results

The flowchart of our study population is shown in Figure 1. As it shows in Figure 1, 9 of 79 assessed patients with acute upper GI bleeding were excluded from the study for various reasons. Ultimately, 49 men (70%) and 21 women (30%) were assigned to the study. The mean age of the study population was (54.34±11.79) years. The most common causes of upper gastrointestinal bleeding was gastric erosion (28 cases, 40%), followed by gastric ulcer (18 cases, 25.7%), duodenal erosion (13 cases, 18.6%), duodenal ulcer (11 cases, 15.7%). Forty-seven patients (67.1%) presented with melena and others (23 cases, 32.9%) had hematemesis. A total of 70 patients with acute upper GI bleeding were randomly divided into 2 groups, including 35 patients in the TXA group and 35 subjects in the control group. There was no statistical difference between groups in baseline characteristics (P>0.05), so the groups were comparable. The patient's characteristics are described in Table 1.

In Table 2, a comparison of admission duration, rebleeding, and need for endoscopy or blood transfusion in the two studied groups are presented. No statistically significant difference was observed regarding admission duration, rebleeding, and need for endoscopy between the two groups (Table 2). It is worth noting that the need for blood transfusion in the TXA group was significantly higher than that in the control groups (P=0.00). None of the patients required surgical intervention.

4. Discussion

GI bleeding remains a major global cause of morbidity and mortality. The initial treatment of upper GI bleeding starts with stopping the bleeding and preventing further bleeding. TXA is an antifibrinolytic agent *via* inhibition of plasminogen activation and is widely used for surgical bleeding. Some studies suggested that TXA is effective for upper GI bleeding management[12,13]. In the present study, TXA did not improve the outcome of patients with bleeding ulcers. Moreover, 60.0% of the patients in the TXA group versus 22.9% of the patients in the control group required

Table 1. Baseline characteristics and clinical data of the study's population.

Variables	TXA group (n=35)	Control group (n=35)	Total (n=70)	t/χ^2	P-value
Age, years (mean ± SD)	53.66 ±11.72	55.02 ±11.98	54.34±11.79	−0.48	0.63
Male [n (%)]	24 (68.6)	25 (71.4)	49 (70.0)	0.06	0.79
Hypotension (systolic blood pressure<90 mmHg) [n (%)]	8 (22.9)	7 (20)	15 (21.42)	0.08	0.77
Hemoglobin (g/dL) (mean ± SD)	9.52±2.12	9.05±1.59	9.29±1.87	1.04	0.3
Pulse rate (beat/minute) (mean ± SD)	94.57±14.50	96.08±14.54	95.32±14.44	0.43	0.66
GI bleeding type [n (%)]					
Hematemesis	10 (28.6)	13 (37.1)	23 (32.9)	0.58	0.44
Melena	25 (71.4)	22 (62.9)	47 (67.1)		

TXA: tranexamic acid; GI: upper gastrointestinal.

Table 2. Comparison of length of stay, rebleeding, blood transfusion, and endoscopic intervention [n (%)].

Variables	TXA group (n=35)	Control group (n=35)	χ^2	P-value
Hospital length of stay (day) median				
<3	20 (57.1)	25 (71.4)	1.55	0.21
⩾3	15 (42.9)	10 (28.6)		
Rebleeding	8 (22.9)	5 (14.3)	0.85	0.35
Need to blood transfusion	21 (60.0)	8 (22.9)	9.95	0.00
Need to endoscopic intervention	9 (25.7)	7 (20.0)	0.32	0.56

blood transfusion during GI bleeding, which was an unexpected finding. Similarly, Tavakoli *et al.* conducted a study to investigate the efficacy of TXA in treating upper GI bleeding[14]. In this double-blind randomized clinical trial, 410 patients were included, and TXA was compared to placebo. There was no significant difference in bleeding, mortality due to bleeding, need for surgery, and need for blood transfusion between the two groups. In 2015, an evidence-based study was conducted in Indonesia to evaluate the therapeutic effect of TXA in patients with upper GI bleeding. The results showed that TXA injection had no significant effect on the outcome of the patients[15].

Furthermore, Karadaş *et al.*[16] found that locally administered single-dose TXA conferred no additional benefits over standard care in patients with upper GI bleeding. Contrary to our study, a double-blind study in patients with severe upper GI bleeding was done to determine the effect of TXA[17]. The authors found a significant reduction in the need for blood transfusion in patients who received TXA. In a study by Rafeey *et al.*[18] the rate of rebleeding was 11.4% in subjects who received topical TXA *via* endoscopic procedures, which was lower than the control group.

In a study conducted by Patchett *et al.*[19] found that gastric juice accelerated GI bleeding both by defective clot formation and by contributing to the lysis of a formed fibrin clot. The authors suggested that acid-dependent factors such as gastric protease were associated with defective clot formation. Thus, although TXA competitively inhibits the activation of plasminogen to plasmin, it has no activity against acid-dependant proteases that are responsible for significant fibrinolysis in patients with upper GI bleeding.

In the study of Karadaş *et al.*[16] the patients with upper GI hemorrhage were administrated with a single 2 000 mg dose of TXA, and no significant changes were observed in mortality, rebleeding, the need for any intervention, and recurrent admission to the emergency department. Similarly, Smith *et al.*[20] reported that TXA does not appear to decrease blood loss and improve clinical outcomes when used for low GI hemorrhage.

Chertoff *et al.*[21] reported that the utilization rate of TXA was low by both surgical and medical intensivists to treat patients with acute upper GI bleeding. Furthermore, guidelines do not recommend the use of TXA in patients with acute upper GI bleeding because of its unclear activity[22]. For this reason, the effectiveness of TXA (1 g, followed by 3 g over 24 h) versus blinded placebo for GI bleeding is being evaluated in a clinical trial named HALT-IT, aiming at recruiting 12 009 adult patients between July 4, 2013, and June 21, 2019[23]. Based on the clinical trial results, TXA did not reduce death but is associated with an increased risk of venous thromboembolic events and seizures. A few studies have investigated the effects of TXA toxicity *in vivo* and/or *in vitro*, and the results are usually contradictory[24,25]. Therefore, further studies are required to confirm the safety of TXA before it can be recommended for standard treatment.

5. Conclusions

Our study was conducted in 2018 when there were a small number of studies in this regard and to our knowledge. The results showed that there is still a long way before a basic conclusion can be achieved on the efficacy of TXA for GI bleeding management. Therefore, future research should be conducted since choosing an appropriate treatment for upper GI hemorrhage patients is not an easy question to be answered by trial and error.

Conflict of interest statement

The authors report no conflict of interest.

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Authors' contributions

H.B.: Study concept and design; H.B. and M.H.: Acquisition of data; A.B.: Analysis and interpretation of data; A.B. and H.B.: Drafting of the manuscript, critical revision of the manuscript for important intellectual content; H.B. and M.H.: Administrative, technical, and material support; H.B.: Study supervision.

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