Am J Transl Res 2024;16(3):925-932
www.ajtr.org /ISSN:1943-8141/AJTR0149473

Original Article

Efficacy and safety of tranexamic acid in the treatment of gastric cancer complicated with upper gastrointestinal bleeding

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Received February 3, 2023; Accepted April 5, 2023; Epub March 15, 2024; Published March 30, 2024

Abstract: Objective: To investigate the efficacy and safety of tranexamic acid (TXA) in preventing upper gastrointestinal (GI) bleeding in patients with gastric cancer. Methods: The clinical data of patients with gastric cancer complicated with acute non-operative GI bleeding treated in the Fourth Hospital of Hebei Medical University from 2020 to 2022 were collected and retrospectively analyzed. The survival status of the patients was followed up by telephone. The dataset of 168 patients was divided into a control group (n=85) and a TXA group (n=83), at a 1:1 ratio. The patients in the control group were treated with esomeprazole, and the patients in the TXA group received additional TXA. The hemostatic effect, rebleeding rate, and mortality of patients were compared between the two groups. The Cox proportional hazard model was used to evaluate the overall survival of patients as well as the related risk factors. Results: The success rate of hemostasis and the normal blood coagulation rate in the TXA group were significantly higher than those in the control group (P=0.003 and P=0.016). The secondary bleeding rate, thrombus formation rate and digestive tract perforation rate in the TXA group were significantly lower than those in the control group (P=0.002, P=0.003 and P=0.035). The improvement of all indicators in the TXA group was better than that in the control group (all P<0.05). For patients with gastric cancer complicated with acute GI bleeding treated with TXA, the Cox proportional hazard model identified III~IV stage, time of TXA treatment, surgical treatment after hemorrhage, and an increase of D-dimer as independent risk factors for upper GI bleeding (all P<0.05). Conclusion: TXA can be an effective treatment for patients with gastric cancer complicated by GI bleeding.

Keywords: Gastrointestinal bleeding, tranexamic acid, gastric cancer, cox proportional hazard model

Introduction

Gastric cancer is a common malignant tumor of the digestive tract, and its incidence is increasing yearly [1]. Gastric cancer complicated with gastrointestinal (GI) bleeding is often acute and severe, which can be life-threatening without timely treatment [2]. Upper GI bleeding refers to bleeding above the duodenal ligament, which is a typical clinical emergency and one of the most common complications of gastric cancer [3]. The incidence of acute GI bleeding in upper digestive tract malignant tumors is about 5% [4]. About 30% of patients with inoperable gastric cancer have neoplastic GI bleeding [5]. Gastric cancer complicated with bleeding is mainly caused by surface injury, erosion, infection, inflammation, ulcer, and wound oozing [6]. When patients with gastric cancer experience considerable tumor necrosis and rapid invasion of larger blood vessels or more neovascularization, it can lead to massive hemorrhage, which is the primary cause of gastric cancer complicated with massive hemorrhage [7]. Upper GI bleeding typically occurs rapidly and can worsen quickly. In severe cases, it can endanger life and affect the therapeutic outcomes and clinical prognosis of patients with gastric cancer [8].

The treatment options for gastric cancer complicated with upper GI bleeding includes conservative drug treatment, such as fasting drinking water, acid inhibition, systemic or local use of hemostatic drugs, correction of anemia, as well as emergency endoscopic treatment, palli-

https://doi.org/10.62347/KOLI5819

ative surgery, extracorporeal radiotherapy, and so on [9]. Traditional drug therapy could reduce the blood circulation in the viscera and decrease the amount of blood in the viscera to achieve the therapeutic effect. However, it can also cause elevated blood pressure, myocardial ischemia, and other symptoms, resulting in dizziness, diarrhea, nausea, and other adverse reactions in patients [10]. The use of tranexamic acid (TXA) can promote hormone secretion in some parts, such as the GI tract and pancreas [11]. It can also reduce the risk of venous thrombosis, decrease the pressure gradient in the portal vein by up to 12%, inhibit GI peristalsis, and promote platelet aggregation [12]. Previous study reported a significantly shortened treatment time for GI bleeding by TXA injection [13].

However, the efficacy and safety of TXA in treating gastric cancer complicated with upper GI bleeding remain unknown. Therefore, this study aimed to evaluate the efficacy and safety of TXA in patients with gastric cancer complicated with upper GI bleeding.

Methods

Research participants

The data collection for this study was carried out with the approval of the Institutional Review Committee of the Fourth Hospital of Hebei Medical University. The current study obeyed the ethical guides of the Declaration of Helsinki and was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University. The medical records of 168 patients diagnosed with gastric cancer complicated with GI bleeding from January 2020 to August 2022 were collected from the electronic medical record system and retrospectively reviewed. Inclusion criteria: (1) Patients were 18 years old or older. (2) Patients diagnosed with gastric cancer and upper GI bleeding based on the *Chinese Expert Consensus on the Difficulties in Diagnosing and Treating Gastric Cancer (version 2020)*. (3) Patients had comprehensive medical records, including medical history, general data, preoperative examination data, and intraoperative results.

Exclusion criteria: (1) Patients were allergic to TXA. (2) Patients had thrombus (acute cerebral infarction, acute myocardial infarction, pulmonary embolism, etc.). (3) Patients had esophageal and gastric varices. (4) Patients had severe heart, lung, kidney, pancreas, or liver diseases. (5) Pregnant and lactating women. (6) Patients were unsuitable to participate in this trial.

Data collection

The hemostatic effect, rebleeding rate, and mortality of the patients were collected.

The criteria for hemostasis were as follows: (1) cessation of hematemesis, melena, or bloody stools; (2) stable blood pressure and vital signs in patients; (3) stable hemoglobin and red blood cell count; (4) absence of active bleeding during preoperative gastroscopy.

Evaluation indicators

The main outcome measure of the current study was the curative efficacy of TXA in patients. The secondary outcome measure was the incidence of thrombotic diseases. The criteria for assessing the curative efficacy were as follows. Significant curative effect was defined as the disappearance of the clinical bleeding symptoms within 24 hours, stable blood pressure, and bleeding cessation under an endoscope. Effective was defined as the disappearance of clinical bleeding symptoms, correction of hypovolemia, stable blood pressure, and stable hemoglobin within 72 hours. Ineffective was defined as persistent bleeding and unstable vital signs leading to continued blood volume loss 72 hours after treatment. The total effective rate was calculated by cases with significant curative effect and effective response. The incidence of thrombotic diseases in the patients was collected and compared. The hemostatic effect was evaluated by monitoring hemoglobin, prothrombin time, activated partial thromboplastin time, international normalized ratio, fibrinogen, fibrin degradation products, and D-Dimmer at 24, 48, and 72 hour after treatment.

Study design and statistical analysis

The 168 patients were divided into a control group (n=85) and a TXA group (n=83), at a 1:1 ratio. The patients in the control group were treated with 80 mg esomeprazole (Life

Technology Biopharmaceutical Co., Ltd.) by intravenous drip, followed by 8 mg/h continuous pumping. The patients in the TXA group were treated with 80 mg esomeprazole (Life Technology Biopharmaceutical Co., Ltd.) combined with 1 g TXA (twice a day, Chongqing Anren Pharmaceutical Co., Ltd.) by intravenous drip, followed by 8 mg/h esomeprazole pumping. The treatment lasted for 72 hours. Categorical data were exhibited as value and (%), and continuous variables were expressed as mean ± standard deviation (SD). For continuous data with normal distribution and homogeneity of variance, the independent sample t-test or Mann-Whitney U was employed for between-group evaluation. The χ^2 test was used for comparison of categorical variables. The total score of each patient was calculated according to the risk calculation formula of the line chart, and the patients were divided into high and low-risk groups. The line chart was constructed according to the risk score, age, sex, TNM stage and other clinicopathological features. The line chart could be used to evaluate the predictive effect of risk scores for patients' survival rates. The calibration curve was used to test the prediction ability of the established line chart model. The DynNom and stargazer package in R language was used to develop the dynamic diagram. The survival differences between the two groups were analyzed and compared by the Kaplan-Meier curve. Multivariate Cox regression was used to evaluate the risk factors of upper GI bleeding in patients treated with TXA, and to build a prediction model. SPSS 22.0 statistical software was used for data analysis and a *P* value <0.05 was considered statistically significant.

Results

Clinical diagnosis and treatment characteristics

According to the *American Cancer Association staging criteria, 8th edition* [14], there were 36 (21.43%) cases at stage I~II, 132 (78.57%) cases at stage III~IV, 141 (83.93%) cases with single GI bleeding and 27 (16.07%) cases with multiple bleeding. A postoperative operation was performed in 79 (47.02%) cases, including radical operation in 59 cases and palliative resection in 20 cases (**Table 1**).

Outcome of patients

By the end of follow-up period, 138 out of 168 cases had died, 30 had survived, and 3 cases were lost to follow-up. The overall survival (OS) of patients was 0.5-84.0 months, with an average of 14. 0 months. The 1-year survival rate was 28.0%, the 3-year survival rate was 18.0%, and the 5-year survival rate was 14.0%. The median survival time of patients with serum alkaline phosphatase >100 U/L (10.0 months) was shorter than that of patients with alkaline phosphatase ≤100 U/L (15.5 months, P<0.01, **Table 1**). The OS of patients with and without operation after hemorrhage was 36.0 and 7.5 months, respectively (P<0.01).

Comparison of therapeutic effects between the two groups

As shown in **Table 2**, the therapeutic effect of the TXA group was significantly better than that of the control group (P<0.05).

Comparison of hemostatic effects between the two groups

As shown in **Table 3**, the hemostatic effect of the TXA group was significantly better than that of the control group (P<0.05).

Comparison of coagulation-associated indicators between the two groups

After treatment, all the blood coagulation indicators in the TXA group improved significantly more than those in the control group (P<0.05, **Table 4**).

Multivariate analysis of risk factors

The comprehensive multivariate analysis of the risk factors for upper GI bleeding in patients treated with TXA showed that III~IV stage, time of TXA treatment, surgical treatment after hemorrhage, and an increase of D-dimer were identified as independent risk factors (**Table 5**, all P<0.05).

Discussion

GI bleeding is a common clinical disease that can vary in severity from mild and self-limited to a life-threatening emergency. The treatment for

Table 1. The outcome and characteristics of patients

Factor	N (%)	Median OS (month)	χ^2	P	HR	95% CI
Age			1.602	0.306	1.460	0.781~2.033
≥60 years	85 (50.60%)	11				
<60 years	83 (49.40%)	13.5				
Sex			0.554	0.731	1.223	0.706~1.895
Female	114 (67.86%)	14.0				
Male	54 (32.14%)	11.5				
TNM stage			21.933	**0.002**	9.336	2.938~25.330
I~II	36 (21.43%)	63				
III~IV	132 (78.57%)	12				
Bleeding times			2.134	0.136	1.654	0.981~2.338
Single time	141 (83.93%)	14				
≥2 times	27 (16.07)	11.5				
D-dimer (mg/L)			6.758	**0.008**	2.651	1.670~5.774
Normal (0~0.55)	29 (17.26%)	46				
Elevated (>0.55)	124 (73.81%)	10				
Hemoglobin (g/L)			4.569	0.140	1.357	1.039~1.998
>90	49 (29.17%)	14				
60~90	66 (39.29%)	14				
<60	53 (77.94%)	11				
Platelets ($\times 10^9$ L^{-1})			4.584	0.933	1.033	1.303~1.947
<100	38 (22.62%)	14				
100~300	85 (50.60%)	14				
>300	45 (26.78%)	12				
Alkaline phosphatase (U/L)			3.495	**0.035**	1.394	0.957~3.454
>100	51 (30.36%)	10				
≤100	117 (69.64%)	15.5				
Post-bleeding treatment			45.782	**0.006**	0.125	0.307~0.985
Operation	79 (47.02%)	36				
Non-surgical	89 (52.98%)	7.5				

P-values were obtained using χ^2 tests for categorical variables. The Wilcoxon or paired t-tests were used for continuous variables. Bold font implies statistical significance. TNM: tumor, node, and metastases.

Table 2. Comparison of therapeutic effects between the control group and the TXA group

	Control (n=85)	TXA (n=83)	χ^2	*P* value
Successful hemostasis	67 (78.82%)	75 (90.36)	1.083	**0.003**
Secondary bleeding	13 (15.29)	14 (16.87%)	0.987	**0.002**
Thrombus formation	11 (12.94)	6 (7.23%)	2.330	**0.003**
Coagulation function is normal	45 (52.94%)	57 (68.67%)	0.068	**0.016**
Perforation of the digestive tract	3 (3.53%)	0 (0%)	1.229	**0.035**

TXA: Tranexamic acid. *P*-values were obtained using χ^2 tests for categorical variables. Bold font implies statistical significance.

GI bleeding is mainly by inhibiting gastric acid secretion and reducing pepsin activity by increasing the pH value in the stomach [15]. In the clinical treatment of upper GI bleeding, inhibition of gastric acid, hemostasis, fluid replacement, and volume expansion are used to improve patients' clinical symptoms and reduce their physical injury [16]. Clinical studies have shown that endoscopic hemostasis is essential in reducing the morbidity and mortality of

Table 3. Comparison of the hemostatic effect between the control and TXA groups

	Control group (n=85)	TXA (n=83)
Significant effect	20 (23.53%)	40 (48.19%)
Effective	47 (55.29%)	35 (42.17%)
Inefficiency	18 (21.18%)	8 (9.64%)
χ^2	1.028	
P value	**0.033**	

TXA: Tranexamic acid. *P*-values were obtained using χ^2 tests for categorical variables. Bold font implies statistical significance.

patients with acute non-varicose upper GI bleeding [17]. Antifibrinolytic drugs such as TXA are used in the routine treatment of upper digestive tract bleeding. TXA is a synthetic analog of lysine used to treat all kinds of bleeding caused by acute or chronic hyperfibrinolysis, whether it is localized or systemic [18]. Low-dose TXA can inhibit plasminogen activation, and high-dose TXA can directly inhibit the activity of plasmin proteolytic enzyme, trypsin, and chymotrypsin [19]. TXA has a high affinity for the lysine binding region of plasminogen, which enables it to competitively inhibit the binding of fibrin lysine to plasmin, thus inhibiting the cleavage of fibrin clot and produce a hemostatic effect [20].

This study retrospectively evaluated the clinical characteristics of 168 patients with gastric cancer complicated with GI bleeding. We found that TXA could effectively shorten the bleeding time, reduce the bleeding, and promote the recovery of body function. Studies have shown that TXA can reduce the rebleeding rate in patients with upper GI bleeding. A meta-analysis has shown that TXA can significantly reduce all-cause mortality from GI bleeding but does not increase the risk of thromboembolic events [21]. Recently, a large international randomized, double-blind, placebo-controlled trial has shown that TXA can reduce the mortality and the risk of venous thromboembolism in patients with GI bleeding [22]. At present, there are no guidelines that provide clear recommendations on the use of TXA for the treatment of GI bleeding [23]. However, another study suggested that TXA was not recommended for patients with acute GI bleeding until further strong evidence emerges [24].

Alkaline phosphatase >100 is a poor prognostic factor for gastric cancer [25]. This study showed that the median survival time of patients with serum alkaline phosphatase >100 U/L was notably shorter than that of patients with alkaline phosphatase ≤100 U/L. Furthermore, multivariate analysis showed that alkaline phosphatase was an independent poor prognostic factor for patients. A recent study has highlighted that increased serum alkaline phosphatase is an independent risk factor affecting tumor-free survival in patients undergoing chemotherapy after radical resection of gastric tumor [26]. It is considered that patients with elevated serum alkaline phosphatase during chemotherapy have an increased risk of recurrence and metastasis [27].

Earlier work indicated that gastric cancer patients complicated with acute GI bleeding or perforation who underwent emergency operation had a better survival rate than those who did not [28]. Another study recommended that gastrectomy can be considered in patients with incurable gastric cancer who have digestive tract obstruction or uncontrollable GI bleeding, but lymph node dissection was not recommended in such cases [29]. This study observed that the survival of patients undergoing operation after hemorrhage was significantly better than that of patients without operation, suggesting that surgical treatment for gastric cancer patients with GI bleeding might improve the survival.

This study performed a comprehensive multivariate analysis of risk factors for upper GI bleeding in patients treated with TXA. The results showed that III~IV stage, time of TXA treatment, surgical treatment after hemorrhage, and an increase of D-dimer were identified as independent risk factors for upper GI bleeding after TXA treatment (all $P<0.05$). As a small fragment of fibrin-specific degradation products, D-dimer can reflect small changes in the coagulation-fibrinolysis system [30]. It was revealed that serum D-dimer level in patients with upper GI rebleeding was significantly higher than that in patients without rebleeding, suggesting that D-dimer can be used as a indexe to predict the risk of rebleeding [31].

The main limitation of this study is that the sample size is relatively small, and this is a

Table 4. Comparison of blood coagulation indexes between the two groups before and after treatment

	Time	Control group (n=85)	TXA group (n=83)	P
PT (s)	Before	11.67±0.89	11.720±0.755	**0.040**
	After	15.87±1.46	12.433±0.910	
aPTT (s)	Before	39.44±3.04	38.490±2.66	**0.005**
	After	46.03±4.55	32.87±2.50	
TT (s)	Before	25.60±5.69	23.40±4.50	**0.001**
	After	23.40±4.33	15.90±2.31	
Fbg (g/L)	Before	2.93±0.78	3.50±0.66	**0.009**
	After	2.18±0.44	3.48±0.78	

TXA: Tranexamic acid; PT: prothrombin time; aPTT: activated partial thromboplastin time; TT: thrombin time; Fbg: fibrinogen. Data were exhibited by n (%) or mean (SD). Bold font implies statistical significance.

Table 5. The Cox proportional hazard regression model of risk factors for upper GI bleeding after TAX treatment

Factor	B	SE	Wald	P	HR	95% CI
TNM stage (III~IV)	1.839	0.750	5.936	0.013	6.227	1.339~20.035
Surgical treatment after bleeding	-1.048	0.403	12.543	0.001	0.349	0.302~0.790
Alkaline phosphatase (>100 U/L)	0.026	0.436	0.033	0.914	1.441	0.509~1.257
D-dimer (Elevated)	0.449	0.401	0.017	0.012	1.049	0.607~1.339

OR: odds ratio; CI: confidence interval; TNM: tumor, node, and metastases.

hospital-based single-center study. Also, there were some limitations in the source of patients. The monitoring time of TEG was short, and most of the patients with upper GI rebleeding treated in the emergency department were in critical condition. The next step in the research process is to increase the number of participants in order to gather more data and confirm the findings.

In this study, we observed that TXA injection as a treatment for GI hemorrhage resulted in significantly better clinical outcomes in the TXA group compared to the control group, suggesting that TXA can be an effective treatment for gastric cancer patients with upper GI bleeding. This study also found that patients with gastric cancer and upper GI bleeding had advanced stages of cancer and a poor prognosis, and active surgical treatment may improve the survival of these patients.

Disclosure of conflict of interest

None.

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