A randomized controlled trial of the effects of local tranexamic acid on mortality, rebleeding, and recurrent endoscopy need in patients with upper gastrointestinal hemorrhage

Adnan Karadaş[a], Nurettin Özgür Doğan[b], Seda Güney Pinar[c], Olcay Yeşil[d], Murat Pekdemir[b], Serkan Yilmaz[b] and Elif Yaka[b]

Objective Tranexamic acid (TXA) is an antifibrinolytic agent used to control bleeding in different circumstances. We conducted a randomized controlled trial to assess the efficacy and safety of locally administered TXA in upper gastrointestinal hemorrhage.

Methods This single-center, double-blind, randomized controlled trial was performed in a tertiary emergency department (ED) in patients presenting with upper gastrointestinal bleeding symptoms between 2016 and 2018. The patients received either 2000 mg of 5% TXA in 100 mL of isotonic saline solution or 100 mL isotonic saline (control group) via the nasogastric route. As a composite outcome, recurrent endoscopy need, rebleeding, surgery need, recurrent admission to the ED, and mortality parameters were evaluated at the end of a one-month period.

Results During the study period, 78 patients were randomized into the TXA group, and 79 patients were randomized into the isotonic saline group. The majority of the bleedings (61%) were in Forrest class 3, and the most frequent cause was peptic ulcer disease. The composite outcome occurred in 25 of the TXA patients (32.1%) and 23 of the isotonic saline patients (29.1%); no statistically significant difference was found between the groups ($P=0.690$). In addition, no statistically significant differences were observed between the TXA and control groups regarding mortality (10.3 vs 12.7%; $P=0.637$), recurrent ED admission (17.9 vs 12.7%; $P=0.357$), or thromboembolic complications (3.8 vs 1.3%; $P=0.367$).

Conclusion Locally administered TXA confers no additional benefit over standard care in patients with upper gastrointestinal hemorrhage. Eur J Gastroenterol Hepatol 32: 26–31

Introduction

Upper gastrointestinal (UGI) hemorrhage occurs frequently and results in substantial clinical and economic burdens, despite medical advances. Mortality due to UGI hemorrhage was found to be 7% among new admissions, and rebleeding rates have been reported at approximately 15% in various populations [1,2]. Many pharmacological treatments can reduce the incidence of rebleeding and the need for surgery or transfusion; however, mortality rates are much more difficult to improve in patients with UGI hemorrhage [3,4]. Still, endoscopic interventions play a significant role in reducing mortality in those patients [5,6].

Although different pharmacological treatment regimens exist for gastrointestinal hemorrhage, the main focus of therapy should be controlling bleeding. As an antifibrinolytic agent, tranexamic acid (TXA) has gained popularity in recent years for different purposes, such as controlling traumatic hemorrhage [7], postpartum vaginal bleeding [8,9], primary intracerebral hemorrhage [10], and epistaxis [11]. Most of the aforementioned trials argue that TXA appears to be a reasonable option for different hemorrhagic conditions and does not increase adverse event rates.

TXA, a derivative of the amino acid lysine, demonstrates an antifibrinolytic effect by inhibiting the action of plasmin. The formation of TXA-plasminogen complexes prevents the degradation of fibrin networks [12,13]. After initially being launched in the late 1960s, TXA began to be used in many fields of medicine and gained importance. To date, many randomized trials have been conducted on TXA use in UGI hemorrhage, but the results of these studies are significantly heterogeneous due to different application routes and dosing regimens [14–21]. A large, randomized, placebo-controlled, multicenter trial has been arranged to discover the real effects of intravenous TXA in UGI hemorrhage and is still recruiting participants [22].

Because TXA was administered in different doses and routes in these studies, it is difficult to reach a definite conclusion about its efficacy. In addition, endoscopic techniques were not used properly in the 1970s and 1980s; thus, the effectiveness of TXA treatment in those trials is

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[a]Department of Emergency Medicine, Balıkesir Atatürk City Hospital, Balıkesir, [b]Department of Emergency Medicine, Faculty of Medicine, Kocaeli University, Kocaeli [c]Department of Emergency Medicine, Zonguldak Atatürk State Hospital, Zonguldak and [d]Department of Emergency Medicine, Kars Harakani State Hospital, Kars, Turkey

Correspondence to Nurettin Özgür Doğan, MD, Associate Professor of Emergency Medicine, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey

Tel: +90 262 303 85 45; fax: +90 262 303 70 03;
e-mail: nurettinozgurdogan@gmail.com

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uncertain. We hypothesized that locally administered TXA could reduce rebleeding and intervention rates in patients with UGI hemorrhage.

Methods

Study design and setting

This single-center, prospective, double-blind, placebo-controlled, randomized trial was carried out in patients with UGI hemorrhage. Reporting of the results was performed according to Consolidated Standards of Reporting Trials (CONSORT) guidelines. The study was conducted from October 2016 to April 2018 in an academic emergency department (ED) that sees approximately 45 000 patients per year. The efficacy and safety of locally administered TXA was compared with isotonic saline in patients with UGI hemorrhage. This study was performed in accordance with the tenets of the Declaration of Helsinki, and Institutional Review Board approval was obtained before the study started. The trial was registered to Clinical Trials (Identifier: NCT02903017). The patients were asked to sign an informed consent form before their enrollment in the study.

Selection of participants

Patients older than 18 years who presented to the ED with symptoms suggestive of UGI hemorrhage were included in the study. Patients were excluded if they refused to give informed consent; had a documented allergy to TXA; had a history of esophageal variceal bleeding or any thromboembolic disease; had gastrointestinal hemorrhage secondary to trauma; or were receiving renal replacement therapy. Patients with variceal bleeding confirmed by diagnostic endoscopy were excluded after randomization.

Methods and measurements

All ED patients were assessed for enrollment in the study at presentation. The randomization process began after the patient showed objective signs and symptoms, such as melena, hematochezia, hematemesis, or vomiting bright red bloody content. After the selection of an eligible patient by a senior emergency medicine resident, the patient was asked to sign an informed consent form to participate in the study and was assigned to the TXA group or the isotonic saline group. The randomization sequence was performed by the study nurse, and the treatment vials were numbered and blinded before they arrived at the patient care area. No worker in the patient care area knew the contents of the vials. The vials were administered by one study investigator. Before administration, a nasogastric tube was inserted, and the placement of tube was confirmed by the patient's caregiver physician. The patient, the nurses, and the physicians, including the endoscopists, were blinded to the administered treatment. After administration, the nasogastric tube was clamped, and this clamp remained in place for 30 minutes after insertion.

Interventions

The randomization schedule was generated using a computer program (http://www.sealedenvelope.com). Eligible patients were randomly assigned in a 1:1 ratio to receive either a single 2000 mg dose of 5% TXA solution (Transamin, Actavis İlaç, İstanbul, Turkey) in 100 mL isotonic saline or 100 mL isotonic saline alone via the nasogastric route. The drug and placebo vials were previously prepared by a blinded study nurse, and the two solutions were identical in physical appearance. Other interventions, including endoscopic techniques, medical therapies, and hospital length-of-stay, were left to the physicians' own decisions.

Outcomes

The primary outcome measure was defined as the composite outcome, including mortality, recurrent UGI hemorrhage (rebleeding), the need for endoscopic or surgical intervention, and ED revisit. All components of the primary outcome measure were assessed by telephone follow-up 30 days after the initial presentation to the ED. Secondary outcome measures were hospital length-of-stay, administered blood products in the ED, and adverse reactions such as anaphylaxis or any thromboembolic event.

Primary data analysis

All statistical analyses were performed with SPSS version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Intention-to-treat analysis was performed for all randomized patients; missing patient responses were treated as bad outcome was occurred. Patients with variceal bleeding were excluded from the analysis after randomization. The intention-to-treat group included patients who left the ED of their own accord and those who did not have an endoscopy performed by decision of the caregiver physician or gastroenterologist. The primary outcome, which was the composite outcome of the critical variables, was assessed with a Chi-square test. Baseline characteristics were compared using Student's *t* test and the Mann–Whitney *U* test for continuous variables and the Chi-square test for categorical variables. All the statistical analyses were two sided. An alpha value of less than 0.05 was considered to be the nominal level of significance.

The sample size was estimated using G-Power for Mac OS X (V3.1.9.2; Universitat Düsseldorf, Germany). According to Wilkins *et al*. [2], the rebleeding rate despite endoscopic techniques is 15% in UGI hemorrhage. Consequently, a total of 104 patients were required to reach 80% power with significance at the 5% level, an increase in the primary outcome measure from 85% in the control group to 100% in the TXA group. An additional 10% ($n = 10$ individuals) was included to account for potential protocol violations ($n = 114$).

Results

One hundred ninety-two patients were assessed for eligibility, and 162 patients were included for randomization. Five patients with active variceal bleeding were not included to the analysis after randomization. Variceal bleeding could not be confirmed before endoscopy and study drug administration, so exclusion was carried out

after randomization. In addition, endoscopy could not be performed in 39 patients for different reasons; these patients were included in the intention-to-treat population. Regarding the TXA and isotonic saline groups, no difference was observed among patients who left the ED ($n=6$) and patients who did not have endoscopy performed by decision of the gastroenterologist or emergency physician ($n=33$). Ultimately, 78 patients from the TXA group and 79 patients from the isotonic saline group were analyzed (Fig. 1).

Characteristics of the study subjects

The baseline characteristics were similar between the groups regarding comorbid diseases (except diabetic predominance in the isotonic saline group), concomitant drug use, hemodynamic parameters, and baseline hemoglobin levels (Table 1).

Endoscopy was able to be performed in 59 patients from both groups. The main etiology of UGI hemorrhage was peptic ulcer disease (51 patients in the TXA group and 52 patients in the isotonic saline group). Other etiologies were drug overdose (five and two patients, respectively) and hemorrhage secondary to malign lesions (three and five patients, respectively). The modified Forrest classification was able to be evaluated in a total of 118 patients who underwent endoscopic examination (Table 2). Most of the patients had class III hemorrhage (clean ulcer base) according to the modified Forrest classification in both groups.

Main results

According to the primary outcome measure, the composite outcome occurred in 25 patients (32.1%) in the TXA group and 23 patients (29.1%) in the isotonic saline group ($P=0.690$). In one month, eight patients from the TXA group and 10 patients from the isotonic saline group died ($P=0.637$). Eventually, no statistically significant

Table 1. Baseline characteristics of the study population

	TXA group ($n=78$)	Isotonic saline group ($n=79$)	P value
Age, years (mean ± SD)	62.9 ± 18.7	63.2 ± 17.3	0.915
Male (*n*, %)	52 (66.7%)	54 (68.4%)	0.821
DM (*n*, %)	10 (12.8%)	22 (27.8%)	0.019
HT (*n*, %)	42 (53.8%)	36 (45.6%)	0.300
CAD (*n*, %)	19 (24.4%)	19 (24.1%)	0.964
History of peptic ulcer (*n*, %)	30 (38.5%)	18 (22.8%)	0.033
History of UGI hemorrhage (*n*, %)	29 (37.2%)	19 (24.1%)	0.074
Drug use			
Proton pump inhibitor (*n*, %)	16 (20.5%)	21 (26.6%)	0.370
Antiplatelet (*n*, %)	25 (32.1%)	24 (30.4%)	0.821
Anticoagulant (*n*, %)	16 (20.5%)	13 (16.5%)	0.222
NSAID (*n*, %)	25 (32.1%)	26 (32.9%)	0.908
Pulse (beat/minute) (mean ± SD)	101 ± 23	97 ± 19	0.237
Systolic blood pressure (mmHg) (mean ± SD)	127 ± 28	127 ± 26	0.920
Hemoglobin (g/dL) (mean ± SD)	9.8 ± 4.3	9.6 ± 3.0	0.828
Platelet count (median, IQR)	243 (193–285)	225 (159–321)	0.330
INR level (median, IQR)	1.13 (1.06–1.21)	1.12 (1.06–1.33)	0.962

CAD, coronary artery disease; DM, diabetes mellitus; HT, hypertension; INR, international normalized ratio; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; TXA, tranexamic acid; UGI, upper gastrointestinal

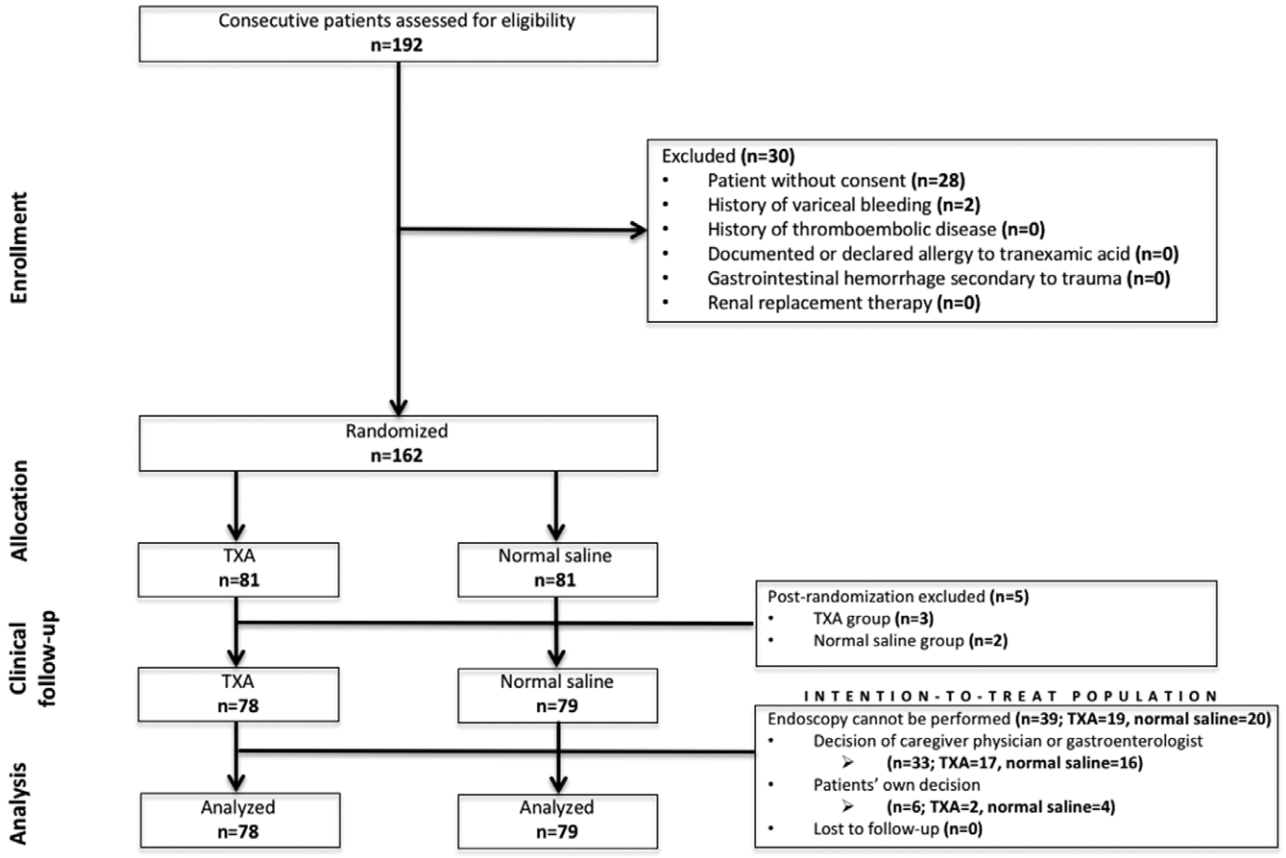

Fig. 1. Patient flowchart. TXA, tranexamic acid.

Table 2. Modified Forrest classification for patients who underwent endoscopic examination

	TXA group ($n=59$)	Isotonic saline group ($n=59$)
Class 1a (*n*, %)	1 (1.7%)	2 (3.4%)
Class 1b (*n*, %)	11 (18.6%)	9 (15.3%)
Class 2a (*n*, %)	7 (11.9%)	4 (6.8%)
Class 2b (*n*, %)	5 (8.5%)	6 (10.2%)
Class 2c (*n*, %)	1 (1.7%)	0 (0.0%)
Class 3 (*n*, %)	34 (57.6%)	38 (64.4%)

TXA, tranexamic acid.

Table 3. Primary and secondary outcome measures

	TXA group ($n=78$)	Isotonic saline group ($n=79$)	*P* value
Composite outcome (*n*, %)	25 (32.1%)	23 (29.1%)	0.690
Mortality (*n*, %)	8 (10.3%)	10 (12.7%)	0.637
Rebleeding (*n*, %)	9 (11.5%)	8 (10.1%)	0.766
Need for endoscopic intervention (*n*, %)	11 (14.1%)	7 (8.9%)	0.303
Need for surgical intervention (*n*, %)	3 (3.8%)	3 (3.8%)	1.000
ED revisit (*n*, %)	14 (17.9%)	10 (12.7%)	0.357
Thrombotic event (*n*, %)	3 (3.8%)	1 (1.3%)	0.367
ED length of stay (hour) median (*n*, %)	10 (5-15)	10 (6-20)	0.161
Hospital length of stay (day) median (*n*, %)	1.5 (0-5)	1 (0-5)	0.871

ED, emergency department; TXA, tranexamic acid.

difference was observed regarding mortality, rebleeding, the need for endoscopic or surgical intervention or ED revisit rates between the groups (Table 3).

The hospital length-of-stay was 1.5 days (IQR: 0 to 5) in patients receiving TXA and 1 day (IQR: 0 to 5) in patients receiving isotonic saline ($P=0.871$). Both groups stayed approximately 10 hours in the ED (Table 3). A total of four thrombotic events were reported for both groups; two patients in the TXA group and one patient in the isotonic saline group experienced pulmonary thromboembolism near the end of the one-month follow-up. One patient in the TXA group was diagnosed with non-ST elevated myocardial infarction after admission to the ward.

Both groups received similar amount of blood products; 34 patients (43.6%) in the TXA group and 39 patients (49.4%) in the isotonic saline group received any blood products ($P=0.468$). A median of 0 (IQR: 0 to 2) packed red blood cells were administered to patients.

Discussion

In the present study, locally administered, a single 2000 mg dose of TXA offers no advantage over standard medical treatments and endoscopic interventions in terms of mortality, rebleeding, the need for any intervention, and ED revisits. TXA did not increase adverse event rates in the study population.

The first study on the role of TXA in gastrointestinal bleeding was published in 1973 by Cormack *et al*. [14]. They found that 1.5 g of orally administered TXA, versus a placebo, may reduce treatment failure and the amount of transfusion needed. In light of these results, they supposed that TXA is absorbed from the gastrointestinal tract despite the presence of blood. After these findings, many clinical trials were carried out on TXA use, and most of the trials compared repeated doses of orally administered TXA (1–2 g) with or without 1 g intravenous TXA [15–21].

In 2008, Gluud *et al*. [23] published a systematic review of the use of TXA in UGI hemorrhage in the aforementioned seven randomized trials [14–20]. Although significant heterogeneity exists between those trials, Gluud *et al*. [23] carried out a random-effects meta-analysis for mortality and rebleeding. They found that TXA reduced mortality significantly compared with a placebo [5 vs 8%; relative risk (RR): 0.61; 95% confidence interval (CI): 0.42 to 0.89]; however, it had no effects on rebleeding (14 vs 16%; RR: 0.88; 95% CI: 0.66 to 1.18), or the need for surgery (10 vs 14%; RR: 0.62; 95% CI: 0.35 to 1.09). In our study population, the mortality rates were higher (10.3% for the TXA group and 12.7% for the isotonic saline group), though this difference was not statistically significant. The difference in mortality may be related to the fact that we evaluated this outcome 30 days after the initial presentation. In the current study, rebleeding rates and the need for surgery were also lower than in previous studies. However, there was no statistically significant difference between the treatment groups regarding rebleeding rates or the need for surgery. The decrease in those rates is probably related to the development of endoscopic techniques over the years, because the previous trials looking at TXA use in UGI bleeding are quite old. One reason for this decrease may be related to the low number of Forrest 3 patients in our study.

After systematic review by Gluud *et al*. [23], a new study was published by Tavakoli *et al*. [21] comparing intravenous TXA (1 g, q6h), locally administered TXA (1 g via a nasogastric tube) following intravenous TXA and a placebo. They argued that the urgent endoscopy need was lower in the second group compared with the first and placebo groups. However, the other outcomes, including mortality, rebleeding, and transfusion requirements, were similar between the groups in the trial of Tavakoli *et al*. [21].

In 2014, a Cochrane review addressed the use of TXA in UGI hemorrhage [24]. It found that TXA appears to have a beneficial effect on mortality (RR: 0.60; 95% CI: 0.42 to 0.87), but a high dropout rate in some of the trials prevented a clear conclusion. Rebleeding and the need for surgery were found to be similar between trials. This review suggests that future trials should include all participants with suspected bleeding or endoscopically verified bleeding, as well as other treatment arms and the coadministration of pump inhibitors and endoscopic therapy. Unfortunately, the previous studies have several disadvantages, including the timing of endoscopy, the lack of advances in endoscopic interventions and the use of different TXA dosing regimens and routes. Therefore, we intended to perform a study to discover the real effects of TXA when used locally in a single-dose form. Similarly, Rafeey *et al*. [25] carried out a study in pediatric patients with UGI hemorrhage. In that trial, TXA was administered directly under endoscopic therapy, and the effects were compared with epinephrine injections. The authors did not find any difference between the two interventions regarding transfusion need, rebleeding, and hospital length-of-stay. The optimal method of topical TXA administration is still under debate; however, direct injection to the lesion side may be more effective than administration through a nasogastric tube.

Our study population included also acute bleeding patients classified with Forrest 1 and 2 bleeding. Those

patients received standard and timely interventions to stop bleeding with or without TXA. Hemodynamic instability is not an excluding criteria for our study, thus actively bleeding patients in Forrest 1 or 2 group might be confused or might have difficulties in speaking or understanding the trial terms. If these conditions existed, the informed consent was signed by the relatives of patients. In addition, patients classified as Forrest 3 bleeding were approximately twice as previously known in the studies (61.0%). According to a recent validation of Forrest classification, 32.5% of the UGI hemorrhage patients are in Forrest 3 group [26]. The high number of Forrest 3 patients in our study may have prevented the real effect of TXA in actively bleeding patients.

The vital parameters including pulse rate and blood pressure were relatively good in our study population. Therefore, endoscopic interventions and rebleeding rates were relatively low. All these findings suggest that there are patients with UGI hemorrhage who are in relatively better clinical condition in our study.

For sample size estimation, we performed an a priori plan to enhance the rebleeding rates and established a difference of 15%. However, after statistical analysis, we realized that the number of patients who benefited from the TXA treatment was not extreme. This problem reduces the post-hoc power of our study. Although this study can be repeated with a large sample size in the future, the clinical difference may remain low between TXA and placebo arms.

Limitations

Our study has several limitations. First, locally administered TXA doses were significantly heterogeneous in previous studies, and most of the studies repeated the TXA doses after the initial TXA dose. We did not perform repeated dosing due to successful endoscopic interventions after initial presentation. Second, we administered TXA via the nasogastric route, which may have resulted in the drug not being able to reach the lesion. Third, we did not differentiate patients according to the underlying reason for UGI hemorrhage. Locally administered TXA may affect specific populations differently, such as patients with gastrointestinal bleeding secondary to gastric cancers or anticoagulant use. Finally, this study was carried out in a single center, which limits the generalizability of our results. In addition, post-hoc power of our study was low. Although there will probably very limited clinical benefit, the study can be repeated in a large population to show statistical difference between TXA and placebo.

Conclusion

The current trial compared the local effects of single-dose TXA in patients with UGI hemorrhage against a placebo. Although there are repeated-dose protocols for TXA use in the literature for UGI hemorrhage, we aimed to administer TXA with current advanced endoscopic techniques and comedications. Our trial showed that a single-dose protocol does not contribute to survival and does not decrease rebleeding or the need for intervention. Future studies involving a combined dosing regimen (intravenous and topical TXA) with endoscopic interventions may clarify the exact role of TXA in UGI hemorrhage.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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