

Evaluation of Tranexamic Acid Effect on Consequences of Upper Gastrointestinal Bleeding in Patients Referring to the Emergency Department; a Randomized Clinical Trial

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ARTICLE INFO	ABSTRACT
<p>Article type: Original article</p> <hr/> <p>Article History: Received: 20-Oct-2019 Accepted: 03-Mar-2020</p> <hr/> <p>Keywords: Intubation, Gastrointestinal Hemorrhage, Tranexamic Acid.</p>	<p>Introduction: Upper gastrointestinal bleeding is one of the major and emergent causes of mortality and morbidity around the world. The tranexamic acid has been raised since years ago as a therapeutic intervention. Therefore, prize of exact and timely treatment of upper gastrointestinal bleeding, the present study aimed to evaluate the effects of systemic tranexamic acid on the possible consequences of upper gastrointestinal bleeding such as need for blood transfusion, admission in intensive care unit (ICU), surgery to control bleeding or eventually short-term mortality.</p> <p>Materials and Methods: This double-blind randomized clinical trial included 88 patients with upper gastrointestinal bleeding in a referral academic gastrointestinal center. Patients with symptoms of upper gastrointestinal bleeding referred to the emergency department were randomly divided into two groups: intervention group (n=45) who treated with tranexamic acid in addition to receive standard therapy for upper gastrointestinal bleeding, and control group (n=43) treated with standard therapy for upper gastrointestinal bleeding and placebo (distilled water).</p> <p>Results: Administration of tranexamic acid along with the standard therapy for upper gastrointestinal bleeding in the intervention group caused reduction in mortality and recurrent bleeding compared to the control group. There is no difference between two groups in need for surgery, hemotransfusion and ICU admission.</p> <p>Conclusion: Due to the beneficial effects of tranexamic acid administration on reducing mortality and bleeding recurrence in patients with upper gastrointestinal bleeding, added this drug to the standard therapy may have a favorable potential for upper gastrointestinal bleeding.</p>
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Introduction

Upper gastrointestinal bleeding is one of the major and emergency causes of morbidity and mortality around the world.

Despite the great advances in medical science, the mortality rate caused by upper gastrointestinal bleeding has remained constant within the past two decades (13-14%) (1,2).

Peptic ulcer is a leading cause of upper gastrointestinal bleeding. A study investigating mortality of patients with upper gastrointestinal bleeding in the UK (2006) demonstrated that the mortality rate was about 15% in these patients (3). Likewise, in Iran, one of the most common causes of patient's referring to the emergency department is gastrointestinal bleeding but there were no true population-based registries for upper gastrointestinal bleeding in Iran (4,5). Large financial burden and the risks of morbidity and mortality associated with upper gastrointestinal bleeding have always necessitated different aspects of prevention, early diagnosis and prompt therapeutic interventions. Based on earlier studies on acute upper gastrointestinal bleeding, the patients treated with tranexamic acid have less need for blood transfusion (6,7). Tranexamic acid is a synthetic analog of amino acid lysine which reduced bleeding (6). The tranexamic acid is normally used to reduce bleeding during heart, bones and joints and liver surgery (8,9). Although drug therapies have improved the treatment process in recent years but mortality rate is still high, so new effective approaches are required in this regard. Numerous articles are available on the effects of tranexamic acid administration in the upper gastrointestinal bleeding whose results showed decrease risk of mortality in patients receiving this drug. Some of these results are uncertain due to low quality of these studies and insufficient sample size involved in this meta-analysis. There are still doubts about its effectiveness and safety. So according to importance of exact and timely treatment of upper gastrointestinal bleeding and lack of study on the effects of systemic tranexamic acid on the upper gastrointestinal bleeding in Iran, we aimed to design a study to look at the effect of

tranexamic acid on the consequences of upper gastrointestinal bleeding.

Our aim in this study was to evaluate the effect tranexamic acid on reduce rebleeding in upper gastrointestinal bleeding, and reduction of ICU admission and in hospital mortality.

Materials and Methods

This double-blind randomized clinical trial included 88 patients with upper gastrointestinal bleeding in 2013 to Imam Reza hospital which is a referral academic gastrointestinal center with about 13000-17000 patients per year. This study broached in moral committee and get ethical justification and ethic code 930035 and RCT number IRCT2014112911956N. In this double-blind study, sample size calculated with Cochrane formula and was 88 patients with gastrointestinal bleeding. The inclusion criteria were all patients admitted to the emergency department proven acute upper gastrointestinal bleeding whom were over 18 years old, hemodynamically stable including the systolic blood pressure greater than 90mmHg and heart rate less than 110 beats per minute and filling out informed consent form. The patients were randomly divided into two groups with allocation ratio of 1:1 and sequentially numbered containers. Block randomization was done with 6block size by emergency medicine specialist who was the guide master of this research and he didn't know in which group each patient was. Then questionnaire completed by the Emergency ward nurse.

1- Intervention group or tranexamic acid group: they were received 1-gram tranexamic acid in addition to standard therapy for upper gastrointestinal bleeding, then one-gram tranexamic acid was administered slow intravenously infusion within 8 hours by emergency medicine assistant who was unaware of the drug administered.

2. Control group: they were treated by standard therapy for upper gastrointestinal bleeding and the placebo (sterile water) by emergency medicine assistant who was unaware of the drug administered.

All patients evaluated for rebleeding by endoscopic examination again within 72 hours of admission, hospitalization in the

intensive care unit (ICU) and mortality rate during hospitalization.

The tools used in this study included demographic information questionnaire, anthropometric indices, inclusion and exclusion criteria appraisal form, informed consent form and medical record of patients and the analyses were not based on intention to treat.

Results

These data were collected over a 12 month period and data descriptions were reported using descriptive statistical indicators such as the frequency and the mean \pm SD within tables and charts. The relationship between quantitative and qualitative variables was performed using t-test and Mann-Whitney U test, ANOVA and Kruskal-Wallis test. Pearson and Spearman correlation coefficients were used to evaluate the correlation among quantitative variables. Data normality was checked through Kolmogorov-Smirnov test. T-test, ANOVA and Pearson test were recruited for data with normal distribution and Mann-Whitney U test, Kruskal-Wallis test and Spearman test for data with non-normal distribution. The relationship between variables was detected

by the Chi-square test and statistical analysis was carried out via SPSS version 11.5 software. istribute quantitative variables was analyzed using Kolmogorov-Smirnov. Parametric tests were employed in the normal variables ($P < 0.05$) and non-parametric tests in the non-normal variables ($P > 0.05$). Descriptive statistics determined properties of research units, and Chi-square tests, t-test and Mann-Whitney as well as Spearman and Pearson correlation coefficients were used to analyze the data.

In statistical analysis of quantitative variables between the two groups (tranexamic acid and placebo) in this study, the mean age of patients in tranexamic acid group was 65.44 and in control group was 64.23, so that there was no significant difference between the two group ($P = 0.756$). The result of t-test showed that a significant relationship can be seen only about three variables of body temperature ($P = 0.019$), systolic blood pressure ($P = 0.010$) and diastolic blood pressure ($P = 0.015$) and there is no significant relationship can be seen for other variables such as age, O₂saturation, Respiratory rate, hemoglobin and hematocrit at the first visit in the Emergency Department (Table 1).

Table 1: Status of people for quantitative variables in two groups

Variable	Group		Total	Significance level*
	Tranexamic acid	Placebo		
	Mean \pm SD	Mean \pm SD	Mean \pm SD	
Age	65.44 \pm 17.97	64.23 \pm 18.42	64.85 \pm 18.1	0.756
O ₂ Saturation	94.28 \pm 2.65	92.81 \pm 4.93	63.56 \pm 3.98	0.082
Body temperature	36.88 \pm 0.38	36.65 \pm 0.52	36.77 \pm 0.47	0.019
Respiratory Rate	17.37 \pm 2.55	18.41 \pm 3.1	17.88 \pm 2.86	0.089
Heart Rate	91.42 \pm 14	91.79 \pm 14.12	91.6 \pm 13.98	0.903
Systolic blood pressure	120.53 \pm 19.36	107.02 \pm 28.27	113.93 \pm 24.93	0.010
Diastolic blood pressure	76.22 \pm 12.98	70.09 \pm 9.93	73.22 \pm 11.93	0.015
Hemoglobin	10.24 \pm 3.09	10.16 \pm 2.67	10.02 \pm 2.87	0.895
Hematocrit	32.57 \pm 7.69	31.67 \pm 7.61	32.13 \pm 8.14	0.606
Platelets	254.97 \pm 96.59	344.53 \pm 542.14	298.73 \pm 385.53	0.279
Prothrombin Time	13.71 \pm 1.77	14.06 \pm 2.29	13.88 \pm 2.04	0.413
t-test*				

The result of Chi-square test for gender distribution between the two groups was: 22 male and 23 female in tranexamic acid group and 28 male and 18 female in control group ($P = 0.385$).

The first group (intervention group, n=45) received tranexamic acid and the second

group administered the distilled water as the placebo (control group, n=43). Overall, 74 patients (84.1%) needed endoscopy for rebleeding evaluation due to clinical suspicions and 14 patients (15.9%) did not need it. In intervention group, 37 peoples (82%) needed endoscopy and 8 patients

(17.8%) did not need it; in the control group, 37 peoples (86%) needed endoscopy and 6 patients (14 %) did not need it. The absolute Risk Reduction of rebleeding was calculated about 0.038 and Relative Risk Reduction 0.044.

Chi-square test results indicated that there is no significant difference between two tranexamic acid and placebo groups in terms of the need for transfusion with hemoglobin level below 7(P=0.853),the need for emergent endoscopy (P=0.624) as well as the need for hospitalization in the intensive care unit (ICU) (P=0.48). Whereas, there is a significant difference between two groups in terms of mortality rate (P=0.025) (Figure 1) and recurrent bleeding (P=0.026) (Figure 2).

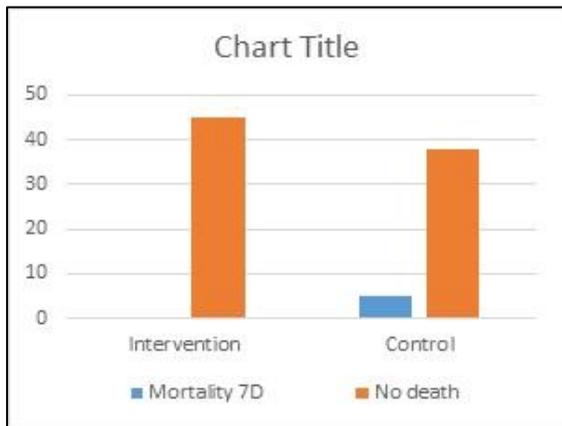


Figure 1: Mortality rate in control and intervention group

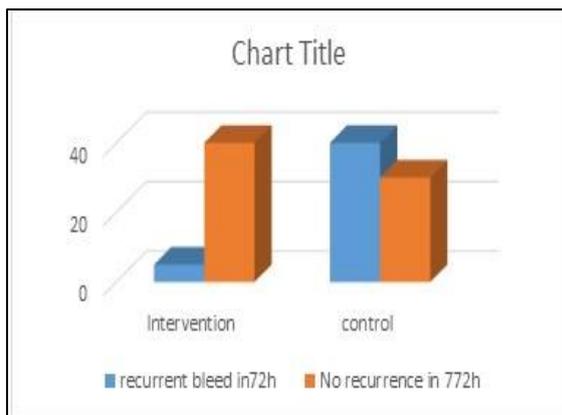


Figure2: Rebleeding in 72 hour in control and intervention group diagnosed by endoscopy

Statistical analysis showed that in the patients group receiving tranexamic acid compared to the control group (placebo), systolic and diastolic blood pressure were significantly different (P<0.05)(Figure 3). However, no significant difference was observed between the two groups in the

other factors such as hemoglobin, hematocrit, platelets, PT, heart rate and respiratory rate.

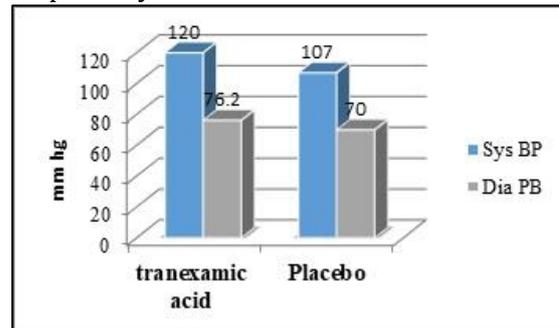


Figure3: Systolic and diastolic Blood pressure in intervention and control group

Discussion

Gastrointestinal bleeding is a common cause of patients' admission to the emergency department. Many financial burdens arising from the need for endoscopy, blood transfusions in patients with upper gastrointestinal bleeding and subsequently the risk of morbidity and mortality have necessitated the need for prevention, early diagnosis and therapeutic interventions. The tranexamic acid has been raised since years ago as a therapeutic intervention due to a decreased need for blood transfusions (4). The results of an endoscopic study conducted on patients with peptic ulcer demonstrated that in patients with characteristics findings such as clean base, active bleeding and visible vessel (with oozing), the possibility of recurrent upper gastrointestinal bleeding is high compared to patients who do not have peptic ulcers. The risk of secondary hemorrhage is 95% among patients with peptic ulcer, which usually occurs in the first 72 hours. In these patients, the mortality rate is high and all hematological parameters and blood pressure are lower.

In recent years, some investigations have been done on the effect of tranexamic acid on reduced bleeding during and after surgery, and cesarean is one of these surgeries that many studies have been conducted about it. The results of a study in 2014 conducted in Egypt showed that administration of tranexamic acid reduces bleeding during caesarean section and then improves hemoglobin levels (10).The use of Tranexamic acid may decrease the risk of

hemorrhage in the gastrointestinal bleeding and need surgery probably due to inhibit fibrinolysis. It has been shown that tranexamic acid caused significant reduction in fibrinolytic activity in granulation tissue and delay in fibrin clot lysis (11).

There is significant and negative relationship between mortality and the use of tranexamic acid; this shows that the use of tranexamic acid can reduce the risk of mortality. In this context, a systematic review conducted by Gluud et al, demonstrated that administration of tranexamic acid has a role in reducing mortality and improving the prognosis of patients with upper gastrointestinal bleeding (8). In addition, the study of Ghosh et al. in 2001 in England suggests that taking tranexamic acid as an anti-fibrinolytic drug has a key role in the homeostasis of blood among patients with upper gastrointestinal bleeding (9). In their study, 100 patients with upper gastrointestinal bleeding were examined in random order. Fifty patients received tranexamic acid and the rest received distilled water (after standard therapy for both groups), like what we do in our study. Then, the group receiving prescribed dosage of tranexamic acid (intervention group) administered 1-gram of tranexamic acid intravenously among 100 people. The results between the two groups showed that there has been a negative and significant correlation among tranexamic acid administration with decreasing the frequency of bleeding and re-bleeding. Administration of tranexamic acid has reduced the recurrent bleeding and mortality. In our study also there is a significant negative correlation between administrations of tranexamic acid and rebleeding in 72 h ($P=0.026$).

Kazemi and colleagues in Iran in a similar study prescribed 15mg/kg intravenous tranexamic acid to patients undergoing total hip arthroplasty surgery as the control group before surgery. Their results showed that hematocrit or hemoglobin levels in the placebo group and control group had no significant difference but the amount of bleeding during and after surgery were significantly decreased. As well, the need for blood infusion had been decreased in these patients (12). In our study, there was no

difference between the two groups for the hemoglobin and hematocrit levels. According to the results of the systematic review by Gluud et al. in 2008, due to declining external and internal validity, more evidence is still required to recommend tranexamic acid as the part of standard therapy for upper gastrointestinal bleeding. The results of the studies in this review showed that due to the lack of significant difference among most of the quantitative variables, none of confounding factors had negative impact on results. It should be noted that none of the 45 patients receiving tranexamic acid had suffered from side effects as well as the use of tranexamic acid in this study had no side effects.

Limitations

Five patients refused to cooperate in our study, therefore excluded from the study. Eight patients reluctant to admit in gastroenterology ward after the admission in emergency department and left the hospital with their own consent, so that they also excluded from our study. This study design and implemented by emergency medicine specialist and some time it seems difficult to follow-up patients to their relevant ward.

Conclusion

The results of present study suggest that taking tranexamic acid medications can prevent drop in blood pressure, reduce recurrent bleeding and decrease mortality in patients with acute upper gastrointestinal bleeding. Thus, this drug is applicable in standard therapy to reduce recurrent bleeding and mortality caused by upper gastrointestinal bleeding. This issue requires further and larger studies for confirmation.

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