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Brief Report

Effect of tranexamic acid on gross hematuria: A pilot randomized clinical trial study

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ABSTRACT

Objective: Local forms of the tranexamic acid have been effective in treating many haemorrhagic cases. So that the aim of the current study is to assess the effectiveness of local tranexamic acid in controlling painless hematuria in patients referred to the emergency department.

Methods: This is a randomized, double-blind clinical trial study, which was conducted on 50 patients with complaints of painless lower urinary tract bleeding during June 2014 and August 2015. The patients were randomly divided into two groups of 25 people each, one group receiving tranexamic acid and the other given a placebo. During bladder irrigation, local tranexamic acid and the placebo were injected into the bladder via Foley catheter. Patients were examined over 24 h in terms of the amount of normal saline serum used for irrigation, level of hemoglobin, and blood in urine.

Results: In this study it was observed that consumption of tranexamic acid significantly decreased the volume of used serum for bladder irrigation ($P = 0.041$) and the microscopic status of urine decreased significantly in terms of the hematuria after 24 h ($P = 0.026$). However, the rate of packed cell transfusion and drop in hemoglobin levels showed no significant difference in both groups of patients (P ˃ 0.05).

Conclusion: The results of this study showed that tranexamic acid could significantly reduce the volume of required serum for bladder irrigation to clear urine, but it had no significant effect on the drop in serum hemoglobin levels.

1. Introduction

Bleeding from the urinary tract is one of the relatively common diseases that are seen in the emergency department (ED) [1,2]. In these patients, in addition to cystoscopy examination, ultrasound and IVP, or even urine analysis and culture, urine cytology, CT urography or CT scan of abdomen/pelvis without contrast or MRI and retrograde pyelograms is required for more accurate evaluation [3-5]. One of the complications of macroscopic hematuria is obstruction of urine flow as a result of the formation of clots inside the bladder, in which case it is necessary for the patient to be provided with a three-way Foley catheter in the size 22–24 French, and the bladder has to be washed to facilitate the expulsion of clots. Although this method is associated with less satisfaction, it is necessary to re-establish the flow of urine [6].

Tranexamic acid is an antifibrinolytic agent and lysine analogue, which results in a block of lysine in the plasminogen that prevents its turning into plasmin. This inhibition reduces tissue plasmin and finally the fibrin [7]. The advantage of local form usage of medication is low levels of drug that leads to reduction of the side-effects [8]. Tranexamic acid leads to the reduction of death from all causes in patients with bleeding from mucous membranes and bleeding surfaces, but reports and evidences demonstrate that the systemic effects of tranexamic acid include anaphylaxis and hypotension, allergic dermatitis, diarrhoea, vomiting, and blurred vision [9,10]. Zahed et al. used tranexamic acid for epigenetic control of epistaxis; and Abrams, in his study, used local tranexamic acid in surgeries of the nose and mouth [11,12].

Based on the above-mentioned topics, No report is available about using the drug locally in spontaneous bleeding from the lower urinary tract. Therefore, we decided to assess the effect of local tranexamic acid to control bleeding in patients with bleeding from the lower urinary tract.

2. Materials and methods

2.1. Study design

This study was a randomized double-blind clinical trial in our emergency department in a large city affiliated to the University Of Medical

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Sciences, from June 2014 through August 2015. Due to the lack of similar studies, this study was performed on 50 patients (25 patients per group).

2.2. Setting and selection of participants

The inclusion criteria covered patients older than 40 years who were referred to the emergency department due to bleeding or clotting with urination, for Foley catheter insertion for washing and ensuring the preparation of urine flow, and consent to participate in research. Exclusion criteria included pregnancy and lactation, and history of thrombosis or thromboembolism, coagulopathy, myocardial infarction or stroke, renal failure, and urinary tract infection. Based on CUA guideline on 1998 "patients over the age of 40 have a significant incidence of pathology such as transitional cell carcinoma and renal cell carcinoma. These lesions are rare in patients under the age of 40. Therefore cystoscopy of young patients with asymptomatic microscopic hematuria is not warranted" [13], because in our ED we didn't able to perform a definite diagnosis based on direct visualization the bladder, we choose this age group. The study was approved by the Ethics Committee of Tabriz University of Medical Sciences by code 1251 on May 5, 2014. This study was registered in the IRCT (Iranian Randomized Clinical Trial) with code IRCT2014072118545N1.

2.3. Randomization and blinding

Patients with complaints of gross hematuria (visible) were enrolled in the emergency department after initial assessments and recording vital signs, history, and physical examination. Randomization was carried out by randomized allocation software. The block model was used for randomization. Fifty patients were divided in two groups of 25.

2.4. Interventions

The protocol of bladder washing was considered for all patients. After catheterization of the bladder, a three-way catheter (Rusch Gold 3 way Hematuria, Teleflex, Perak, Malaysia) was used to start bladder washing. For one group, tranexamic acid (500 mg/5 ml, Tranexip, Caspian Tamin Pharmaceutical Company, Rast, Gilan, IR Iran), and for the other distilled water, were used for bladder washing. The cost of tranexamic acid in our country is 50 cents per vial. Tranexamic acid and distilled water labelled 1 and 2 respectively were prepared in separate 5 ml syringes by the executor and the person performing the washing was the assistant chief of emergency medicine who did not know the contents of the syringes.

In the intervention group, 500 mg tranexamic acid was dissolved in 100 ml of normal saline solution (Shahid Ghazi Pharmaceutical Co, Tabriz, IR Iran) and during the bladder washing a three-branch catheter was inserted in the bladder, while in the other group distilled water in volume of 100 ml of normal saline solution was used. In both groups, urinary flow was closed for 15 min by clamping the catheter to the drug to apply its effect locally. Then after the specified time urinary flow was opened. After the intervention, patients were hospitalized in the urology department for 24 h. Washing was continued until transparency of the urine flow.

2.5. Methods of measurement

The normal saline volume for washing in both groups was recorded in litres and the reduction rate of blood in the urine was evaluated with urine test strip (Analyticon, Lichtenfels, Germany). The amount of blood in the primary urine sample of the patient was reviewed before washing; and then an hour, 3 h, and 24 h after the drug administration, the blood loss in urine was measured as the rate of positive urine test strips (from 1+ to 4+ where 4+ means more blood in the urine). Changes in hemoglobin levels in patients were recorded on three occasions (at the beginning, after 6 h, and after 24 h). In this study, the per-protocol analysis strategy was used. Fig. 1 shows a flowchart of patients in the study.

2.6. Analysis

The data collected was encoded and analysed using SPSS 17.0 statistical software and described on the prevalence (percentage) with a mean (SD). To assess for the normal distribution of data, the Kolmogorov-Smirnov test was used. For qualitative comparison of data, Chi-square test and, for quantitative comparison, independent sample's *t*-test, were used. Where necessary in the non-normal distribution of data, the median, and the first and third quartiles were used to describe the data and Mann–Whitney *U* test was also used for quantitative comparison of data between the two groups. The repeated measurement of ANOVA test was used for comparison of a bit variable changes over time in a group. In all the tests mentioned, the level of significance was defined as *P* value less than 0.05.

3. Results

3.1. Characteristics of study subjects

This study was conducted on 50 patients with hematuria gross. After assessment in terms of inclusion and exclusion criteria, patients were divided into two groups of 25. The mean age of patients was 62.62 ± 11.30 years. In terms of gender composition, 43 (86%) of the patients were male and the rest were female. Table 1 shows the demographic and laboratory findings of patients in the two groups.

3.2. Outcome

Average normal saline to wash the bladder in patients was 10.76 ± 4.32 l (range: 21–5 l) which was used within 24 h for the urine to clear and become transparent. Table 2 shows laboratory findings and the amount of normal saline used to wash in both groups.

To evaluate changes in hemoglobin during 24 h, repeated measurement of ANOVA method was used. Fig. 2 shows the curve of hemoglobin shifts in the three time periods (moments before the intervention, and six and 24 h after). As it is determined in the graph, the downward slope of hemoglobin changes in the control group is more than the intervention group, but these changes were not statistically significant ($P = 0.062$).

3.3. Limitations of the study

In this study, there are two major limitations: one was a lack of cooperation of patients for the study; the other one was that patients who were discharged after initial treatment in the emergency department and were satisfied, did not follow up; these two factors resulted in the low sample size of our study.

4. Discussion

In this study, it was observed that consumption of tranexamic acid reduced the washing serum volume significantly ($P = 0.041$). Also, the microscopic state of urine significantly decreased in terms of the hematuria ($P = 0.026$) but failed to significantly reduce transfusion of packed cell and increased hemoglobin levels ($P > 0.05$).

Reviewing the literature showed that there was no study similar to the present study, hence the articles were examined with the use of tranexamic acid. In the study by Peces et al. [10], the effect of intravenous tranexamic acid on reduction of hematuria in patients with polycystic kidney was examined and the results revealed massive bleeding control and decrease in hemoglobin drop. In two studies, the impact of topical tranexamic acid for reduction of bleeding after transurethral resection of the prostate (TURP) had successful outcomes [9,14].

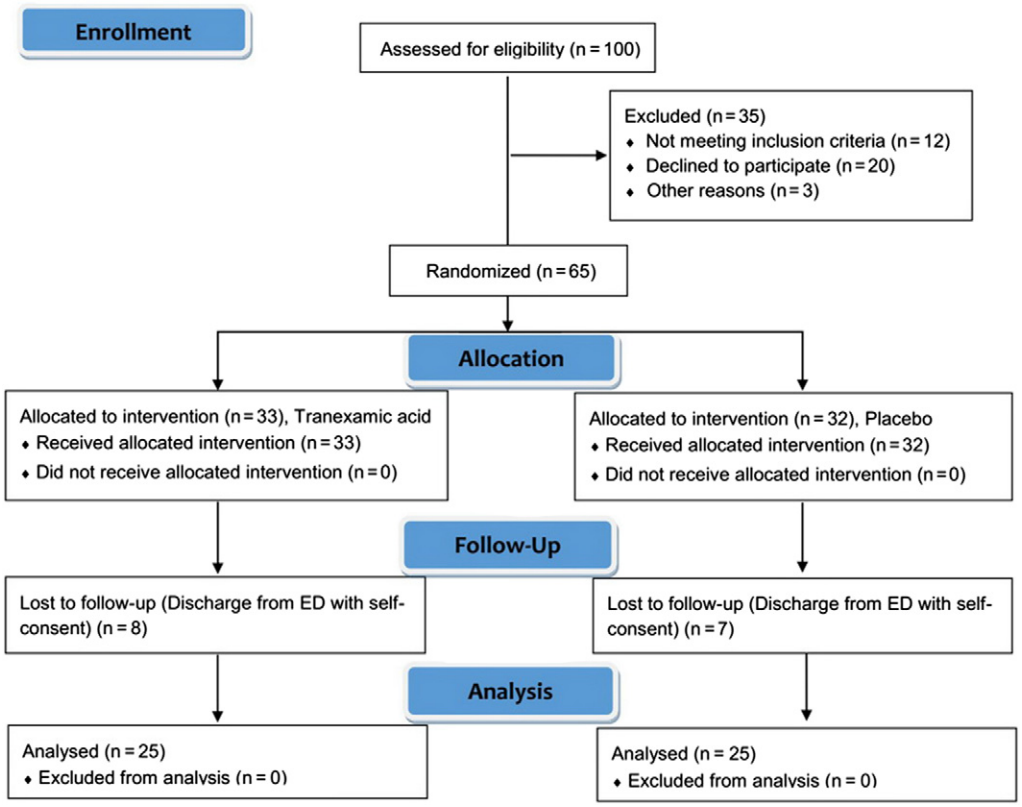

Fig. 1. Flowchart of our study.

In our study, it was found that the decrease in hemoglobin 24 h after local usage of tranexamic acid within the bladder was lower than the control group but the amount was not significant statistically. Also in patients treated with the serum containing tranexamic acid, the need for washing serum to clear the urine is less.

According to the results of the current study, it can be concluded that the use of tranexamic acid reduces the amount of washing serum to urine but it has not any effect on drop in hemoglobin or packed cell transfusions. Given that the study was a pilot study with a small sample

Table 1
Comparison of demographic and laboratory findings in both groups of patients.

Variable	Group 1 (tranexamic acid)	Group 2 (placebo)	*P* value
Age	62.36 ± 9.71	62.88 ± 12.89	0.87[a]
Sex (male/female)	21/4	22/3	1.00[b]
History of hematuria			0.75[b]
Yes	17 (68.0%)	19 (76.0%)	
No	8 (32.0%)	6 (24.0%)	
Median of duration of hematuria (days)			0.08[c]
First quartile	1.00	2.00	
Median	2.00	4.00	
Third quartile	3.50	6.50	
Mean	3.28	4.68	
Clot in urine			0.56[b]
Yes	17 (68.0%)	14 (56.0%)	
No	8 (32.0%)	11 (44.0%)	
Needs for packed cell transfusion			0.08[b]
Yes	16 (64.0%)	9 (36.0%)	
No	9 (36.0%)	16 (64.0%)	
Laboratory finding			
First hemoglobin level (g/l)	11.04 ± 2.89	11.52 ± 3.11	0.57[a]
Urea (mmol/l)	53.48 ± 12.20	56.44 ± 14.03	0.43[a]
Creatinine (mg/dl)	1.48 ± 0.65	1.54 ± 0.57	0.73[a]
Amount of blood in urine (first time)			0.65[b]
+	0 (0.0%)	0 (0.0%)	
++	1 (4.0%)	2 (8.0%)	
+++	8 (32.0%)	10 (40.0%)	
++++	16 (64.0%)	13 (52.0%)	

[a] Independent sample's test.
[b] Chi square test
[c] Mann–Whitney *U* test.

Table 2
Comparison of laboratory findings and used normal saline volume to wash in the two groups.

Variable	Group 1 (tranexamic acid)	Group 2 (placebo)	P value
Amount of irrigation serum (liter)	9.52 ± 4.13	12.00 ± 4.22	0.04[a]
Hemoglobin level in 6 h after intervention (g/l)	10.48 ± 1.96	10.92 ± 2.27	0.47[a]
Hemoglobin level in 24 h after intervention (g/l)	10.00 ± 1.70	9.56 ± 1.87	0.39[a]
Amount of blood in urine (1 h after intervention)			0.68[b]
+	0 (0.0%)	0 (0.0%)	
++	2 (8.0%)	2 (8.0%)	
+++	13 (52.0%)	13 (52.0%)	
++++	10 (40.0%)	10 (40.0%)	
Amount of blood in urine (3 h after intervention)			0.39[b]
+	0 (0.0%)	0 (0.0%)	
++	7 (28.0%)	4 (16.0%)	
+++	12 (48.0%)	11 (44.0%)	
++++	6 (24.0%)	10 (40.0%)	
Amount of blood in urine (24 h after intervention)			0.02[b]
+	0 (0.0%)	0 (0.0%)	
++	10 (40.0%)	4 (16.0%)	
+++	12 (48.0%)	10 (40.0%)	
++++	3 (12.0%)	11 (44.0%)	

[a] Independent sample's test.
[b] Chi square test

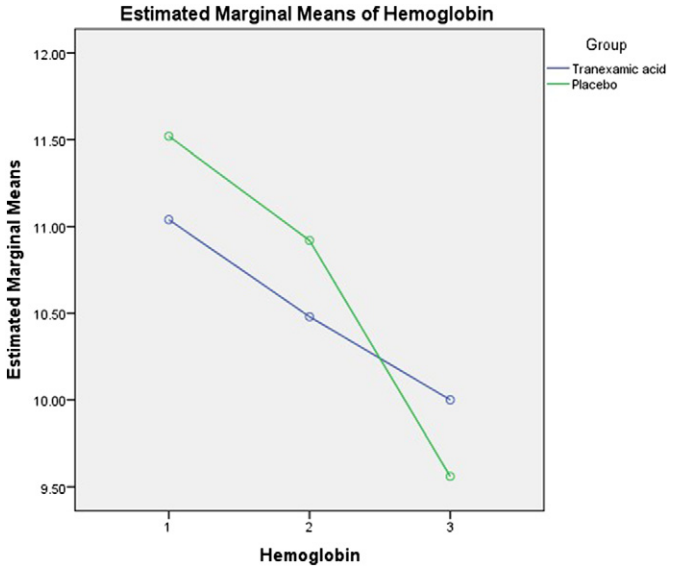

Fig. 2. The curve of hemoglobin shifts in the three time periods.

size, further studies evaluating the results of the current study with a larger sample size is recommended.

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Authors' contributions

All authors have read and approved the manuscript. AA, HJB, and MA performed the data collection, literature review, and drafting the manuscript. FR undertook the major parts of the study design and performed the statistical analysis.

Conflict of interest

The author(s) declare that they have no competing interest.

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