Original Article

Effects of Tranexamic Acid on Bleeding and Hemoglobin Levels in Patients with Staghorn Calculi Undergoing Percutaneous Nephrolithotomy: Randomized Controlled Trial

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What's Known

- Percutaneous nephrolithotomy (PCNL) has been considered a standard procedure for the management of most kidney stones.
- Incidence of renal hemorrhage during PCNL is relatively high.

What's New

- Tranexamic acid (TXA) can reduce the risk of bleeding in PCNL and attenuate the drop in hemoglobin levels in the postoperative period.
- For the first time, we evaluated the effects of TXA on PCNA by considering the stone size as a significant factor in bleeding.

Abstract

Background: The incidence of renal hemorrhage during percutaneous nephrolithotomy (PCNL) is high. We sought to evaluate the effects of tranexamic acid (TXA) on bleeding and hemoglobin levels of patients with staghorn calculi treated with PCNL.

Methods: In a double-blind clinical trial, 120 patients with staghorn calculi candidated for PCNL in Alzahra Hospital between January 2014 and November 2017, Isfahan, Iran, were classified into two groups in terms of the stone size (>4 cm and <4 cm). The patients in both groups were then randomly assigned to receive either 1 g of TXA intravenously or normal saline. (The generation of random numbers was done by computer.) Thus, there were four groups of 30 patients each. The transfusion rate, the mean volume of blood loss, the operative duration, and the hemoglobin level were compared between the intervention and control groups for each stone-size category. Statistical analysis was performed using SPSS, version 19. The paired and independent *t* test and the Pearson coefficient correlation were used, and a P value less than 0.05 was considered statistically significant.

Results: The mean volume of blood loss was significantly higher in the control group patients than in those receiving TXA, in both stone-size categories (P=0.00). There was no significant difference in the postoperative hemoglobin level between the intervention and control groups, in both stone-size categories (P=0.26 and P=0.10, respectively). In addition, the mean volume of blood loss increased significantly with an increase in the operative duration (P=0.00).

Conclusion: TXA reduced the risk of bleeding during and after PCNL and attenuated the drop in the hemoglobin level in the postoperative period. Longer operative procedures were associated with an increase in the bleeding volume.

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Keywords ● Tranexamic acid ● Staghorn calculus ● Bleeding ● Hemoglobin

Introduction

Urolithiasis is the third most common disease in urology clinics after urinary tract infections and prostate disease.[1] There has been an increased prevalence of kidney stones in the United States, with the prevalence rate approaching 7% in female and 10.3% in male individuals in 2010.[2] The prevalence of kidney stones in Iran is reported to range from 1.9% to 5.7%,[1] and this increase is related to dietary and lifestyle factors.[3] Staghorn calculi are branched stones composed of cystine, uric acid, or mixed with other components.[4] Calcium oxalates or phosphate stones rarely grow in a staghorn configuration.[4] Untreated staghorn calculi can be life-threatening.[5]

Recent years have witnessed an increase in the use of percutaneous nephrolithotomy (PCNL) in the treatment of kidney stones.[6-8] PCNL is currently a standard and minimally invasive procedure for the management of most large stones.[9] It is employed in the surgical treatment of large renal stones (>2 cm), staghorn calculi, lower pole stones, cystine calculi, stones associated with urinary tract abnormalities, and in cases where other treatment modalities have failed.[10, 11] This procedure is associated with short periods of hospitalization compared with anatrophic nephrolithotomy.[6, 11, 12] However, complications occur in a quarter of patients (23.3%) following PCNL.[9] Bleeding is one of the most common and worrisome complications insofar as bleeding during and after PCNL still constitutes a major cause of morbidity.[13]

Tranexamic acid (TXA) is one of the derivatives of lysine and inhibits the activation of plasminogen to plasmin. An antifibrinolytic agent,[14] TXA is used for the treatment of certain types of bleeding, including hematuria, and bleeding caused by surgical procedures and traumas.[15, 16] Previous research on surgical patients has demonstrated the efficacy of TXA in reducing blood loss, hemoglobin levels,[17] and the number of patients requiring transfusion.[18] Nevertheless, the use of this antifibrinolytic agent is associated with complications such as vision problems, nausea, vomiting, diarrhea, and thromboembolic events.[16-18]

The incidence and prevalence of kidney stones are on the rise in Iran, and only a few studies have thus far been performed on the impact of TXA on bleeding in patients with staghorn calculi undergoing PCNL. We, therefore, conducted the present study to evaluate the effects of TXA on bleeding and hemoglobin levels in this group of patients.

Patients and Methods

This double-blind clinical trial was performed on patients with staghorn calculi who underwent PCNL in Alzahra Hospital, Isfahan, Iran, between January 2014 and November 2017. Totally, 120 patients were selected according to the following formula (confidence level: 95%):

$$n = \frac{\left(Z_1 - \frac{\alpha}{2} + Z_1 - \beta\right)^2 \times [P - (1 - P)]}{d^2}$$

Formula 1

The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences and was registered in the Iranian Registry of Clinical Trials (IRCT code: IRCT20180209038673N1). Patients over 18 years of age with staghorn calculi and a serum creatinine level of up to 1.5 mg/dL were considered eligible for the study. The exclusion criteria were comprised of intravascular coagulation, skeletal disorders, acquired color vision, subarachnoid hemorrhage, drug sensitization, and non-consumption of aspirin, warfarin, or vitamin E. Informed consent was taken from all the patients, who were thereafter placed in groups A or B (stone size <4 cm and >4 cm, respectively). The choice of these two stone sizes was based on the latest papers in this field.[12] Additionally, the risk of bleeding in patients with a stone size of greater than 4 cm is higher than that in patients with a stone size of less than 4 cm. Via a *computer program* to generate proper *random numbers,* the patients in both groups were randomly divided into two subgroups (i.e., four groups of 30 patients each), with one subgroup receiving 1 g of TXA intravenously for 12 hours until discharge and then orally following discharge for 1 week and the other subgroup (control group) receiving 1 g of normal saline until discharge. Both the patients and the researcher were blinded in the current study. The mean volume of blood loss, the operative duration, the duration of hospitalization, the pre- and postoperative hemoglobin levels, and the transfusion rate were recorded for all the patients and subsequently compared between the two intervention and their respective control groups, as well as according to the stone size. The bleeding volume was evaluated using the following formula:

$$\frac{HCT - 30 \times Weight \times \begin{cases} 80 & Childeren \\ 75 & Female \\ 70 & Male \end{cases}}{HCT}$$

Formula 2

The CONSORT flowcharts of the patients in groups A and B are depicted in figures 1 and 2.

The statistical analyses were performed

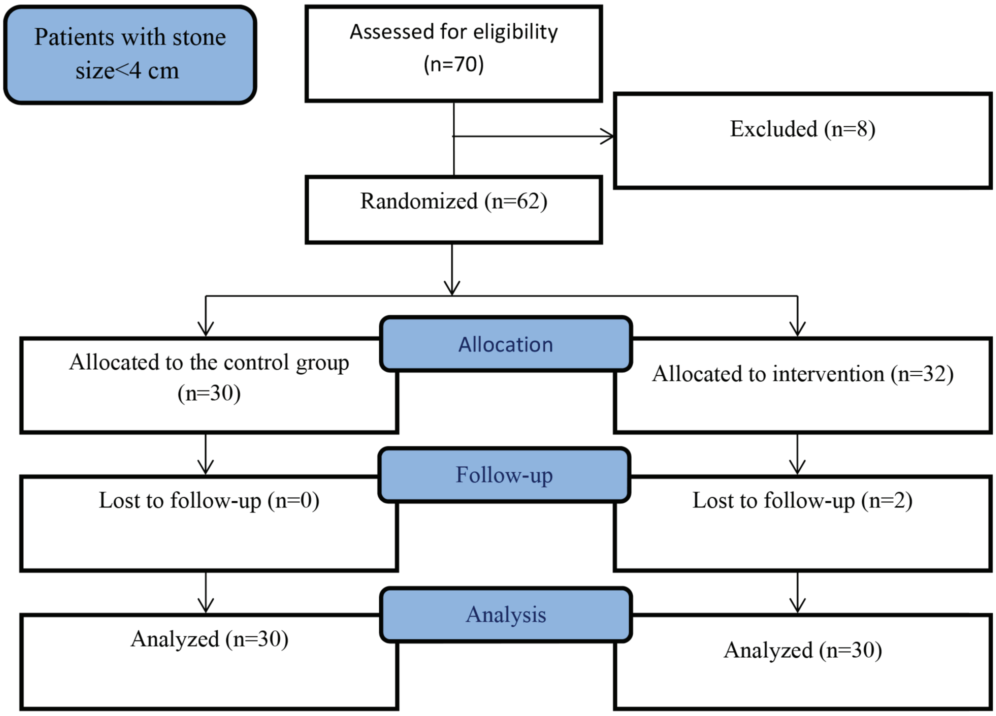

Figure 1: CONSORT flowchart of the patients with a stone size of less than 4 cm in Alzahra Hospital between 2014 and 2017.

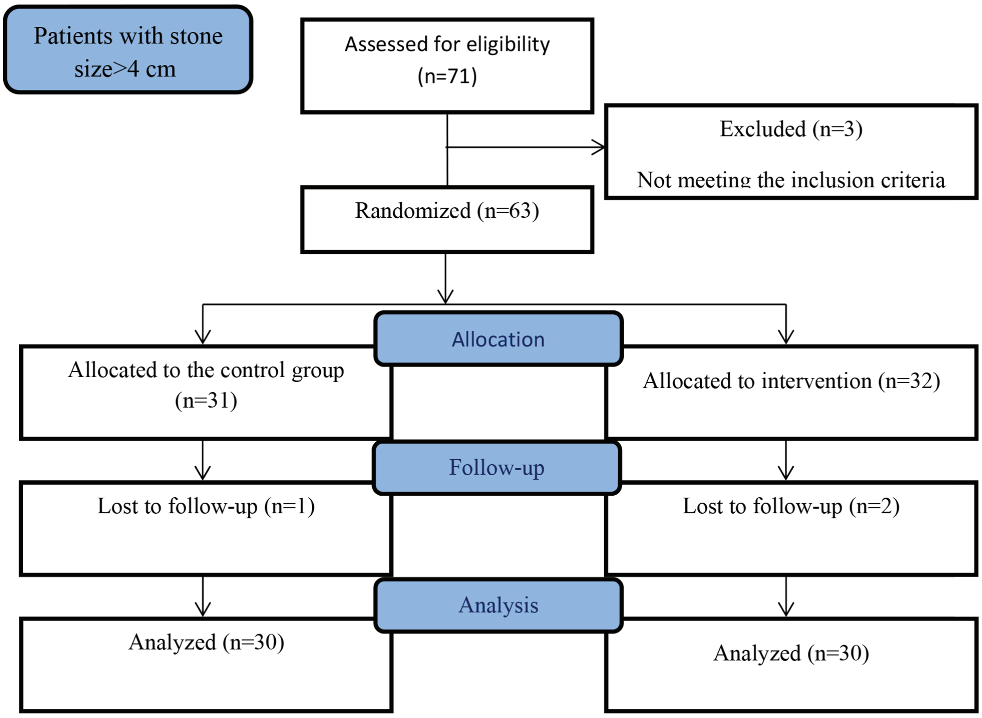

Figure 2: CONSORT flowchart of the patients with a stone size of greater than 4 cm in Alzahra Hospital between 2014 and 2017.

using SPSS, version 21. The variables were compared between the two groups using the independent *t* test, and the variables before and after treatment were compared using the paired sample *t* test. The Pearson coefficient correlation was applied to determine the correlations between the variables.

Results

The comparisons of the parameters of age, the stone size, and the body mass index (BMI) between the two groups of patients are presented in table 1.

With respect to gender, 83.3% and 70% of

Table 1: Comparisons of the parameters of age, the stone size, and the body mass index between the two groups of patients with staghorn calculi in Alzahra Hospital between 2014 and 2017

Parameter	Intervention group	Control group	P value
Age			
1	42.80±15.10	43.60±14.30	0.85
2	41.10±13.20	41.50±13.34	0.90
Stone size			
1	4.20±0.30	4.00±0.27	0.17
2	2.40±0.57	2.55±0.69	0.37
Body mass index			
1	25.67±1.54	25.10±1.81	0.06
2	23.70±1.90	24.70±1.43	0.16

1: stone size>4 cm; 2: stone size<4 cm

the patients with a stone size of more than 4 cm in the intervention and the control groups were male, respectively, whereas 70% and 80% of the patients with a stone size of less than 4 cm in the intervention and control groups were male, correspondingly. There were no significant differences between the two groups in terms of age, the BMI, and the stone size (P>0.05) (table 1).

The comparisons of the mean hemoglobin levels before and after PCNL between the two groups of patients are illustrated in table 2.

As is shown in table 2, there was a significant difference between the intervention and control groups in terms of the hemoglobin levels before and after PCNL (P<0.00) in that a significant decrease was observed in the mean hemoglobin level after treatment compared with before treatment (P<0.00).

The comparisons of the mean hemoglobin levels between the intervention and control groups of patients are demonstrated in table 3.

As is shown in table 3, the postoperative hemoglobin level was significantly higher in the patients receiving TXA (P=0.00), and there was a significant drop in the postoperative hemoglobin level in the control group (P=0.00).

The comparisons of the hemoglobin level between the intervention and control groups after PCNL in both stone-size categories indicated no statistically significant difference (P=0.26 and P=0.10, respectively). As regards the mean volume of blood loss during PCNL in the intervention and control groups, the results showed that the mean value was significantly higher in the control group patients (675±104.30 cc) than in those receiving TXA (584.30±154.51 cc) (in the group with the stone size>4 cm) (P=0.00). The mean blood loss volume was significantly higher in the control group patients (500±121.32 cc) than in those receiving TXA (298±95.30 cc) (in the group with the stone size<4 cm).

A significant correlation was observed in the operative duration and the mean volume of blood loss between the intervention group (P<0.00 and r=0.70) and the control group (P=0.00 and r=0.64) (in the group with the stone size>4 cm). There was also a significant correlation in the operative duration and the mean volume of blood

Table 2: Comparisons of the mean hemoglobin levels before and after PCNL between the two groups of patients with staghorn calculi in Alzahra Hospital between 2014 and 2017

Stone Size \ Group	Group	Before PCNL	After PCNL	P value
Stone size>4 cm	Intervention group	14.38±1.49	12.27±1.70	0.00<
	Control group	13.57±1.80	10.80±1.66	<0.00
Stone size<4 cm	Intervention group	13.43±1.36	12.50±1.57	<0.00
	Control group	14.02±1.56	11.47±1.70	<0.00

PCNL: Percutaneous nephrolithotomy

Table 3: Comparisons of the mean hemoglobin levels between the intervention and control groups of patients with staghorn calculi in Alzahra Hospital between 2014 and 2017

Stone Size \ Hemoglobin	Hemoglobin	Intervention group	Control group	P value
Stone size>4 cm	Before	14.38±1.49	13.57±1.82	0.06
	After	12.27±1.71	10.81±1.62	0.00
Stone size<4 cm	Before	13.43±1.36	14.02±1.56	0.10
	After	12. 5±1.57	11.47±1.71	0.00

loss between the intervention group (P=0.99 and r=0.72) and the control group (P=0.00 and r=0.67) (in the group with the stone size<4 cm).

With regard to the need for blood transfusion in the patients with the stone size of less or more than 4 cm, the results revealed no significant difference between the intervention and control subgroups (60±22.80 mL vs. 135±31.54 mL) in group A (P=0.29) and no significant difference between the intervention and control subgroups (150±34.10 mL vs. 270±43.58 mL) in group B (P=0.24). Moreover, concerning blood transfusion, there were no statistically significant differences between the two intervention groups (P=0.23) and between the two control groups (stone size>4 cm and stone size<4 cm) (P=0.17).

Regarding the mean duration of hospitalization, the results demonstrated no statistically significant differences between the intervention and control subgroups (4.21±0.64 days vs. 3.6±0.40 d) in group A (P=0.10) and between the intervention and control subgroups (4.33±0.6 days vs. 4.50±0.62 days) in group B (P=0.30).

Furthermore, the regression analysis showed that the stone size did not affect the hemoglobin level (P=0.37).

$Hb=10.90+0.76x_1-0.15x_2$

Discussion

In the current study, we observed a statistically significant difference in the post-PCNL hemoglobin level between the intervention and control groups in both stone-size categories (i.e., >4 cm and <4 cm). In other words, the mean postoperative hemoglobin level was significantly higher in the patients receiving TXA than in those receiving normal saline. The mean volume of blood loss was lower during surgery in the TXA group than in the control group. Ferner and colleagues[19] reported that severe bleeding during PCNL was due to the high-flow arteriovenous network surrounding the collecting system and that using TXA decreased the bleeding and hemoglobin drop. Santosh and others[17] reported that the use of TXA in PCNL was associated with decreased blood loss and lower complication rates. Additionally, they reported that the decreased bleeding during PCNL led to better visibility, shorter operative times, and lower volumes of intraoperative irrigation. EL Nahas and coworkers[20] concluded that bleeding during and after PCNL was a major cause of morbidity[20] and reported that the complication rate of PCNL was between 7% and 27% and transfusion was required in 18% of their patients. In their study, conducted from 2013 to 2016, Prakash and colleagues[21] selected 141 patients at a mean age of 52 years who underwent PCNL for renal calculi so as to evaluate the efficacy and safety of TXA with respect to bleeding. They observed that the mean hemoglobin drop in the TXA group was significantly less than that in the control group and concluded that not only was PCNL a minimally invasive method to treat kidney stones larger than 2 cm but also TXA as a safe and advantageous antifibrinolytic agent in the treatment of PCNL was associated with less bleeding and minor complications. Another study also reported a significant reduction in the transfusion rate of patients treated with high-dose TXA.[20] Kumar and coworkers[17] (2012) found that TXA decreased bleeding during PCNL. In addition, they reported that TXA bound to plasminogen with high affinity and acted as a competitive inhibitor to inhibit plasminogen conversion into plasmin; this inhibition decreased fibrin degradation and, thus, reduced bleeding. The final conclusion by Kumar and others was that the use of TXA during PCNL was safe and was associated with decreased blood loss. Brown and colleagues[22] demonstrated the efficacy of TXA in decreasing postoperative bleeding and blood transfusion in coronary artery bypass operations and reported that the administration of TXA immediately after surgery conferred minor advantageous effects. Dunn and others[23] observed that TXA decreased bleeding after oral surgery in their patients with hemophilia and concluded that TXA was a useful drug for lessening postoperative blood losses in some surgical modalities. What was also reported in their investigation was that TXA appeared to have decreased the mortality rate. In the current study, the transfusion rate in the intervention group was lower than that in the control group. However, this reduction was not statistically significant, which might be explained by the small sample size. Mihai and colleagues[24] reported that the transfusion rate in their TXA group was lower than that in their control group and concluded that the use of TXA in PCNL was safe, inexpensive, and affordable. Huang and others[15] reported that TXA decreased blood loss and the requirement for blood transfusion in their patients undergoing orthopedic surgery. Staphan and coworkers[25] reported that the transfusion rates during or after PCNL were from 11.2**% to** 17.5%. Zufferey and colleagues[26] evaluated the role of TXA in hip fracture surgery and reported that the transfusion rate was 42% with TXA administration and 60% with a placebo. They also reported that the preoperative hemoglobin level, age, and the type of surgery were the risk factors for blood transfusion. Kumar and coworkers[17] in another study selected 200 patients undergoing PCNL and classified them into two equal groups. Group I received TXA and group II did not receive TXA. The results of their study showed that the rate of blood transfusion was lower in the TXA group. They concluded that the use of TXA in PCNL decreased the need for blood transfusion and reported that TXA was associated with lower intraoperative and perioperative complication rates. The most worrisome postoperative complication in their study was hematuria. In light of the results of the current study and other studies, it appears that TXA can decrease bleeding and could, therefore, be used effectively for the prevention of bleeding.

In the present study, we observed a significant association between the mean volume of blood loss and the duration of surgery. Akman and others[27] also reported that multiple factors, including diabetes and the operative duration, increased blood loss during PCNL. Elsewhere, Yamaguchi and colleagues[28] reported that the operative duration was one of the factors affecting bleeding during PCNL. In that respect, Ball and coworkers[29] reported that a longer duration of surgery caused increased morbidity and mortality and concluded that an increased operative duration could predict infectious complications, including sepsis, pneumonia, urinary tract infections, and septic shock.

In our study, the stone size (<4 cm and >4 cm) did not affect the postoperative hemoglobin level in either the TXA or the saline group. In contrast, Ferner and others[19] reported that the factors associated with increased blood loss included the stone surface area and the stone type.

The facts that our study population was selected totally randomly and all the surgical procedures were performed by one surgeon are the salient strengths of the present study. What can also be deemed a strong point of this study is the elimination of possible confounding factors through the exclusion of children and the elderly as well as patients with risk factors such as high creatinine levels and heart disease. It is also worthy of note that whereas some studies have evaluated the effects of TXA on PCNL, we are the first to assess the effects of TXA on PCNL by considering the stone size as a significant factor in bleeding. Future studies with larger sample sizes and consideration of other factors such as the combination of rocks will shed more light on this issue.

Conclusion

Our results showed that TXA reduced the risk of bleeding during and after PCNL and attenuated the drop in the hemoglobin level in the postoperative period. Longer operative procedures were associated with increased bleeding volumes. Furthermore, no statistically significant association was found between the stone size and bleeding.

Conflict of Interest: None declared.

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