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**Research Article**

# Effect of Topical Tranexamic Acid on Postoperative Hemoglobin Level in Patients Undergoing Percutaneous Nephrolithotomy; A Double-Blind Randomized Clinical Trial

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**ABSTRACT**

**Background**: Percutaneous nephrolithotomy is a gold standard for kidney stones larger than 2 cm in diameter. One of the complications of percutaneous nephrolithotomy is hemorrhage, for which intravenous Tranexamic acid can be used. This study was performed to compare the rate of postoperative hemoglobin decrease in patients undergoing percutaneous nephrolithotomy following topical Tranexamic acid in nephrostomy compared with control group.

**Methods and materials**: In this double-blind clinical trial study, 90 patients undergoing percutaneous lithotomy were randomly divided into two groups, topical Tranexamic acid and control (without Tranexamic acid injection) group. In the intervention group, 1 gr of Tranexamic acid was diluted in 100 ml of normal saline and injected into the nephrostomy drain (not intravenously) immediately after surgery. The catheter is then clamped for 30 minutes to prevent leakage of Tranexamic acid. After data collection, data were entered into SPSS version 16.

**Results**: The mean age of patients in this study was 45.21 years and no significant difference was observed between the two groups (P= 0.013). The rate of hemoglobin loss after surgery was significantly different from the preoperative hemoglobin level in the two groups, so that the hemoglobin loss was -1.9±1.28 in the Tranexamic acid group and -3.07±1.20 in the control group (P=0.001). In comparison between the groups estimated using independent t test, the difference in hemoglobin after surgery in the two groups was statistically significant (P = 0.001). Regarding stone free rate, the two groups had a similar condition and about 70% of patients were eventually discharged with a stone free condition. The time of surgery was not significantly different between the two groups, so that in the Tranexamic acid group it was 82.37±33.57 minutes and in the control group it was 87.15±33.39 (P <0.001).

**Conclusion**: This study showed that topical application of Tranexamic acid after the end of percutaneous nephrolithotomy can prevent hemoglobin loss in patients with low preoperative hemoglobin level, as well as in cases of longer surgical length or large and numerous stones which is more likely to bleed can reduce the amount of bleeding.

**Keywords:** *Tranexamic acid, Hemoglobin, PCNL*

## Introduction

Urinary stones are the third most common disease of the urinary tract following urinary tract infections and pathological disorders of the prostate (1). It is estimated that about 2-3% of the population has urinary tract stones, which in some studies has been reported up to 5 percent (3-1). Urinary stones are recurrent and there is no definitive way to prevent them, but simple surgical methods have been developed to remove the stone (3-5).

The prevalence of urinary stones in Iran is 2-3% (6, 7). The incidence of kidney stones increases with age. Men are more likely than women to have nephrolithiasis; a ratio of 1.15 was reported in Iran in this regard (8). In addition to the high prevalence of nephrolithiasis, recurrence of this disease is also common in the world and it is estimated that 50% of stones will recur within 10 years (9). Percutaneous nephrolithotomy (PCNL) is the gold standard for nephrolithiasis larger than 2 cm (10, 11). PCNL is a treatment for nephrolithiasis larger than 2-3 cm in diameter, multiple renal calculus stones, large ureteral stones, renal diverticulitis stones, and other type of stone which have not been successful in crushing by using Extracorporeal Shock Wave Lithotripsy (ESWL) (12-15).

In fact, the discovery of less invasive surgical methods has brought about fundamental changes in urology (16, 17). Percutaneous nephrolithotomy as a minimally invasive method has low morbidity and mortality (18). Of course, endoscopic urology is also associated with complications such as bleeding and excessive absorption of washing fluids into the body through the opening of veins or peritoneum, which can cause hemodynamic, electrolyte and sometimes hormonal instability (19, 20).

Tranexamic acid is one of the ways to reduce bleeding during surgery (21). The effect of Tranexamic acid in different doses has been observed in several studies on reducing intraoperative bleeding and reducing the need for transfusion in orthopedic, neurosurgery, cesarean section, heart and oral and surgeries (22-25). In Iran,

Tranexamic acid has been used to reduce bleeding and the need for transfusion in urological, cardiac, gynecological and cesarean surgeries, spinal and neurosurgery and orthopedics (22-30).

According to a recent study by Mohammadi et al, intravenous Tranexamic acid injection showed preventive effect on the bleeding in patients undergone PCNL (31).

However, in another study conducted by Mohammadi et al, no significant difference was observed between the groups using Tranexamic acid and control (32). Therefore, a study was performed to evaluate the changes in hemoglobin in patients undergoing PCNL after Tranexamic acid injection in nephrostomy in comparison with patients without injection.

## Methods and materials

In this randomized clinical trial, 90 patients who underwent percutaneous nephrolithotomy were randomly (using random allocation software) assigned in the two groups of Tranexamic acid and control (without Tranexamic acid). According to a study of Mohammadi et al, (30), using the formula of mean difference in two independent groups and considering 15% attrition, significance level of 5% and power of 80%, 45 patients was considered for each group of (total 90 patients) (Chart 1).

Inclusion criteria were ASA class <III, age between 18 and 80 years and lack of coagulopathy. Exclusion criteria were need for installation of Double J and blood transfusion during surgery and having a history of ureteral stent implantation due to ureteral dilatation.

In the intervention group, 1 gr of Tranexamic acid was diluted in 100 ml of normal saline and inserted into a nephrostomy drain (not intravenously) immediately after injection.

The ureteral catheter was then clamped for 30 minutes to prevent leakage. The variables studied in this study were hemoglobin after surgery, age, and sex and body mass index.

Hemoglobin changes were measured before surgery and 48 hours after surgery. Stone location and stone size based on radiological studies were extracted from the patient's radiological reports.

The design of this study was a double-blind intervention and patients were unaware of the study groups and the data were coded to the statistical analyst so the study was double-blind.

After entering the data into SPSS version 21, frequency and percent for qualitative variables and mean and standard deviation for quantitative variables were reported.

Chi-square test and independent t-test were used for analytical purposes. Paired t-test was used for group comparison. $P< 0.05$ was considered significant. The present research was approved by the University Ethics Committee (#IR.UMSU.REC.1398.422) and registered in the Iranian Registry of Clinical Trials (#IRCT20180625040232N2). This investigation was in accordance with the Declaration of Helsinki.

## Results

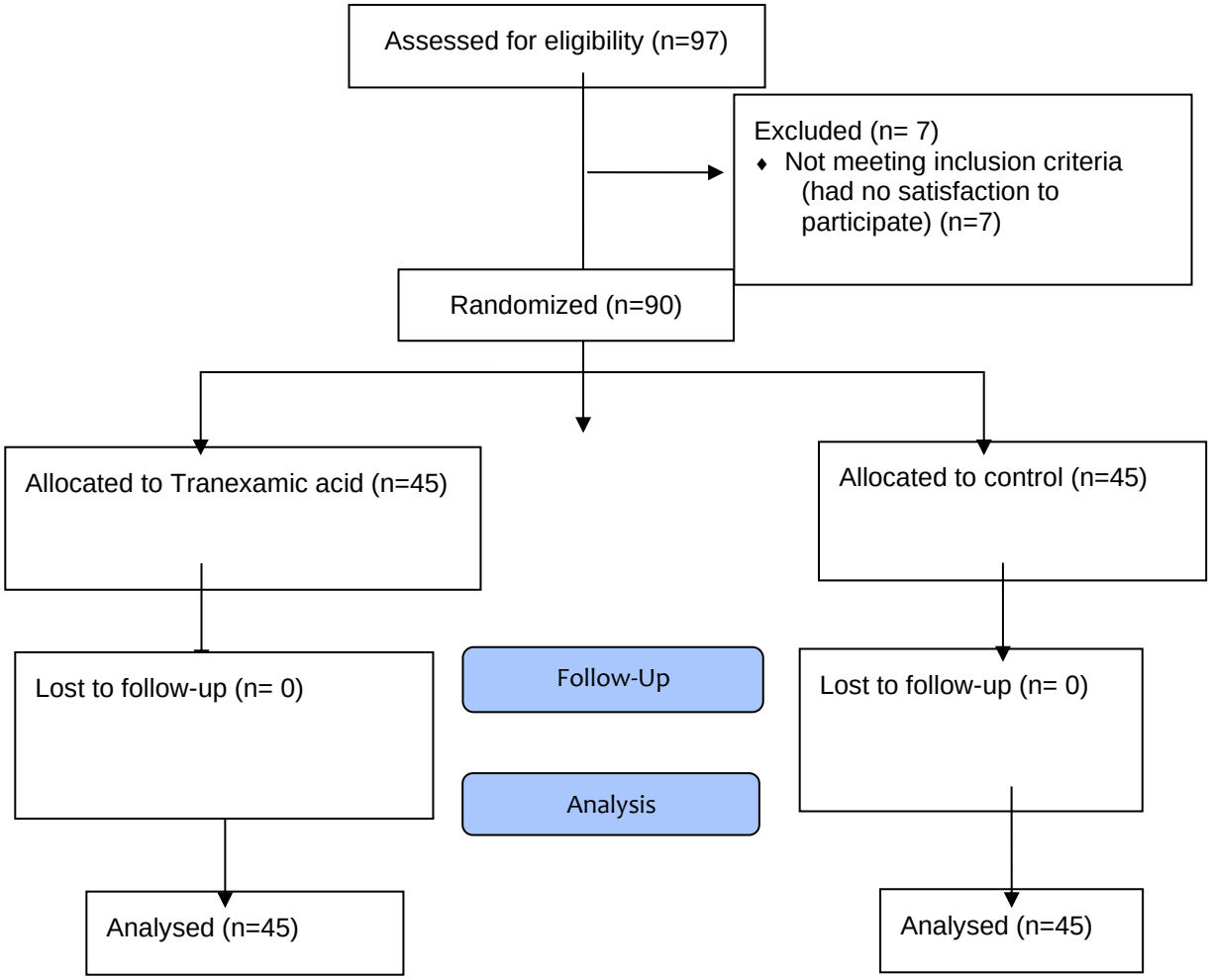



**Chart 1:** CONSORT flowchart diagram

In this study, the mean age of the patients was 45.21±11.69 years (age range: 16 to 76 years) and no significant difference was observed between the two groups in terms of age (p = 0.013). It should be noted that patients (82 patients) underwent spinal anesthesia and 3 patients in the intervention group and 5 patients in the control group underwent general anesthesia. Weight of the patients in the two groups was not statistically different (p = 0.068). Regarding gender, 55.6% of the patients were male and 44.4% were female, but there was no significant difference between the two groups (p = 0.671). In this study, the mean surgery time of patients in the intervention (82.37 minutes) and control (87.15 minutes) groups was not significantly different (p = 0.500). The rate of decrease in hemoglobin after surgery was significantly different between the two groups, so that the decrease in hemoglobin in the Tranexamic acid (-1.9 ± 1.28) and in the control group (-3.07± 1.20) (t = 7.141, p = 0.001) was statistically different. The difference in hemoglobin drop after surgery in the two groups was statistically significant (p = 0.001). According to Stone free rate, the two groups had a similar situation and it was about 75% in both groups. The time of surgery was not significantly different between the two groups (p> 0.001). In this study, the mean changes of patients' hemoglobin in this study were strongly and significantly different in the intervention (-1.91 mg/dl) and control (-3.07 mg/dl) groups (p <0.001). The mean number of patients performing ESWL in this study was not significantly different in the intervention and control groups (p=0.382). The mean number of stones in this study was not significantly different in the intervention and control groups (p=0.569). The mean volume of washing serum of patients in this study was not significantly different in the intervention and control groups (p= 0.522). The mean time of radiation (seconds) between the intervention and control groups of patients in this study was not significantly different from the intervention and control groups (p = 0.745) (Table 1).

**Table 1**: Mean and standard deviation of quantitative variables between intervention and control groups

| Variable | Group | Mean | SD | t | P value |
|---|---|---|---|---|---|
| Age | With Tranexamic acid | 43.35 | 9.78 | -1.517 | 0.013 |
| | Without Tranexamic acid | 47.06 | 13.18 | | |
| Weight | With Tranexamic acid | 79.55 | 13.78 | 1.845 | 0.068 |
| | Without Tranexamic acid | 73.88 | 15.31 | | |
| Surgery time | With Tranexamic acid | 82.37 | 33.57 | -0.677 | 0.500 |
| | Without Tranexamic acid | 87.15 | 33.39 | | |
| Hemoglobin difference | With Tranexamic acid | -1.9178 | 1.28 | 7.141 | <0.001 |
| | Without Tranexamic acid | -3.0733 | 1.20 | | |
| Number of ESWL | With Tranexamic acid | 2.77 | 2.65 | 0.884 | 0.382 |
| | Without Tranexamic acid | 2.11 | 1.96 | | |
| Number of stone | With Tranexamic acid | 1.76 | 0.75 | -0.572 | 0.569 |
| | Without Tranexamic acid | 1.86 | 0.86 | | |
| Irrigation serum (L) | With Tranexamic acid | 7.71 | 6.11 | -0.642 | 0.522 |
| | Without Tranexamic acid | 9.08 | 13.02 | | |
| Radiation time (Second) | With Tranexamic acid | 79.46 | 52.11 | 0.326 | 0.745 |
| | Without Tranexamic acid | 76.20 | 41.65 | | |

In this study, the mean stone density, stone size, SSD, KV radiation of patients in the intervention and control groups were not significantly different (p <0.05) (Table 2).

**Table 2**: Comparison of dimensional characteristics of stones between intervention and control groups

| Variable | Group | Mean | SD | t | P value |
|---|---|---|---|---|---|
| Stone density HU | With Tranexamic acid | 670.24 | 291.39 | .718 | 0.475 |
| | Without Tranexamic acid | 625.90 | 281.21 | | |
| Stone size | With Tranexamic acid | 24.35 | 9.69 | -.829 | 0.411 |
| | Without Tranexamic acid | 28.04 | 28.22 | | |
| SSD | With Tranexamic acid | 76.84 | 32.06 | -1.480 | 0.143 |
| | Without Tranexamic acid | 85.55 | 22.81 | | |
| KV | With Tranexamic acid | 92.38 | 12.85 | -.075 | 0.940 |
| | Without Tranexamic acid | 92.63 | 17.44 | | |
| mA | With Tranexamic acid | 7.27 | 1.50 | -.721 | 0.473 |
| | Without Tranexamic acid | 7.46 | 0.73 | | |

In terms of history of stone-related symptoms leading to surgery, the two groups did not show significant differences in flank pain, urinary tract infection, and nausea (p = 0.561). There was no significant difference between the two groups in terms of disabilities associated with diabetes, hypertension, asthma and hydronephrosis (p <0.05) (Table 3; Figures 1 and 2).

**Table 3**: Comparison of the history of symptoms, comorbidity and hydronephrosis between intervention and control groups

| Variable | | Group | | X2 | P value |
|---|---|---|---|---|---|
| | | Intervention | Control | | |
| History of symptoms | Flank pain | 31 (68.9%) | 32 (71.1%) | 1.971 | 0.578 |
| | UTI | 1 (2.2%) | 0 (0.0%) | | |
| | Asymptomatic | 10 (22.2%) | 12 (26.7%) | | |
| | UTI and Vomiting | 3 (6.7%) | 1 (2.2%) | | |
| Comorbidity | DM | 0 (0%) | 1 (2.2%) | 1.182 | 0.757 |
| | HTN | 8 (17.8%) | 13 (28.9%) | | |
| | Asthma | 0 (0%) | 1 (2.2%) | | |
| | Lymphoma | 1 (2.2%) | 0 (0 %) | | |
| | Coagulopathy history | 2 (4.4%) | 1 (2.2 %) | | |
| | DM+HTN | 6 (13.3%) | 10 (22.2 %) | | |
| | None | 28 (62.2 %) | 19 (42.2 %) | | |
| Hydronephrosis | Yes | 32 (71.1%) | 36 (80.0%) | 0.390 | 0.532 |
| | No | 13 (28.9%) | 9 (20.0%) | | |

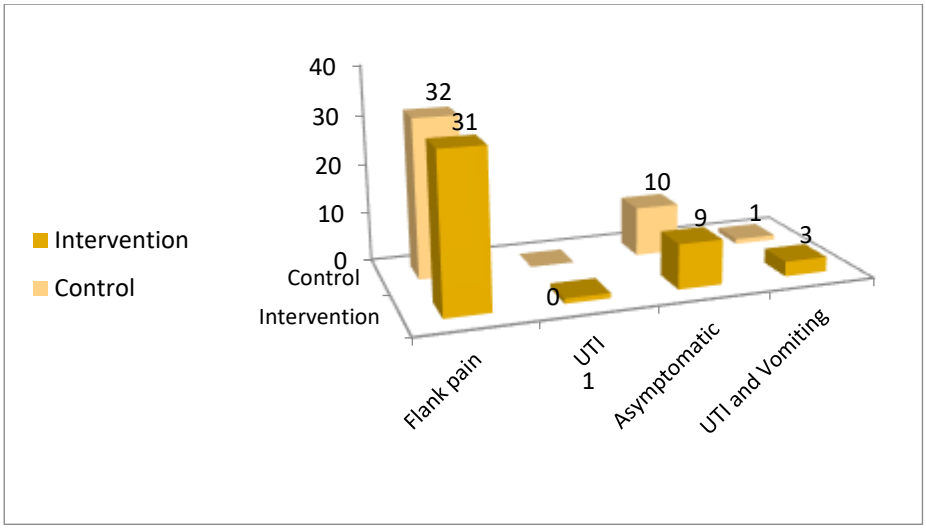
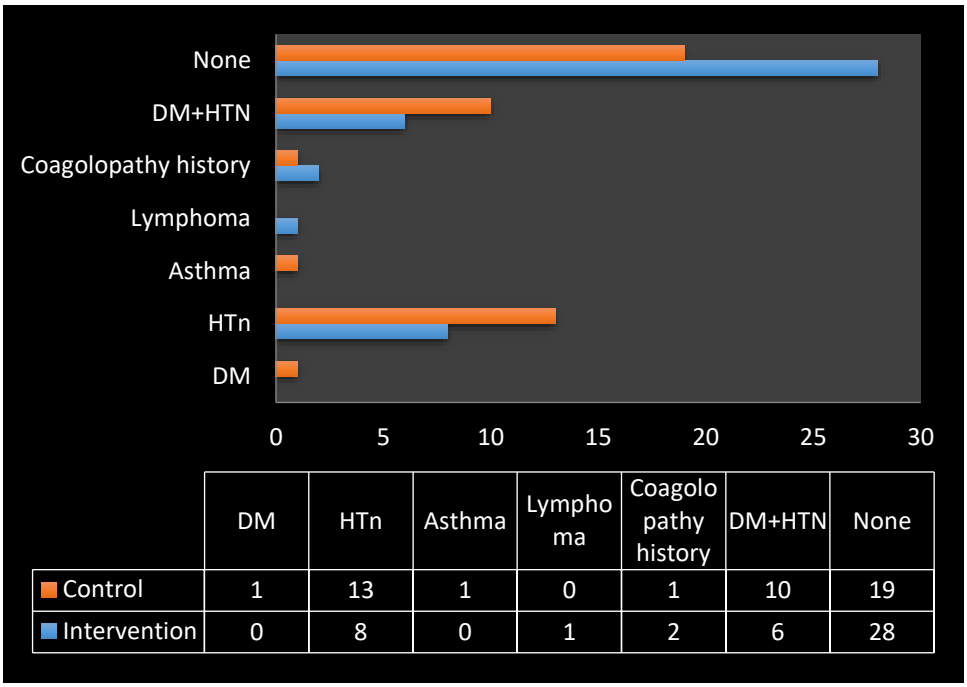



**Figure 1**: Comparison of symptom history profile between intervention and control groups




| | DM | HTn | Asthma | Lympho ma | Coagolo pathy history | DM+HTN | None |
|---|---|---|---|---|---|---|---|
| Control | 1 | 13 | 1 | 0 | 1 | 10 | 19 |
| Intervention | 0 | 8 | 0 | 1 | 2 | 6 | 28 |

**Figure 2**: Comparison of comorbidity disease between intervention and control groups

In terms of stone side, ESWL history, opacity, stone location, number of tracts and access failure, the results did not show significant differences between the two groups ($p < 0.05$). In terms of stone location, the most common stone location was Pelvic + Inferior calyce (32 patients). Also, 47 patients had stones on the right and 43 patients on the left. In the control and intervention group, the majority of patients (93.3%) had a tract. The most common place of access in the control and intervention group was the lower calyce (Table 4).

**Table 4**: Comparison of stone profile and opacity characteristics and stone access between intervention and control groups

| Variable | | Group | | X2 | P value |
|---|---|---|---|---|---|
| | | Intervention | Control | | |
| Side | Right | 22 (48.9%) | 25 (55.6%) | 0.401 | 0.673 |
| | Left | 23 (51.1%) | 20 (44.4%) | | |
| Opacity of stone | Yes | 25 (55.6%) | 27 (60%) | 0.689 | 0.407 |
| | No | 20 (44.4%) | 18 (40%) | | |
| Place of stone | Pelvic | 13 (28.9%) | 15 (33.3%) | 2.363 | 0.669 |
| | Inferior calyce | 10 (22.2%) | 10 (22.2%) | | |

| | | | | | |
|---|---|---|---|---|---|
| | Pelvic+Inferior calyce | 17 (37.8%) | 15 (33.3%) | | |
| | UPJ | 4 (8.9%) | 2 (4.4%) | | |
| | UPJ+Inferior calyce | 1 (2.2%) | 3 (6.7%) | | |
| Number of tract | One | 42 (93.3%) | 42 (93.3%) | 0.000 | 1.000 |
| | Two | 3 (6.7%) | 3 (6.7%) | | |
| Access failure | Yes | 1 (2.2%) | 0 (0%) | 1.011 | 0.315 |
| | No | 44 (97.8%) | 45 (100%) | | |
| Site of access | Superior calyce | 4 (8.9%) | 4 (8.9%) | 0.082 | 0.960 |
| | Middle calyce | 7 (15.6%) | 8 (17.8%) | | |
| | Inferior calyce | 34 (75.6%) | 33 (73.3%) | | |

Regarding RH, 81% of patients in the intervention group and 88.9% of patients in the control group were positive and there was no significant difference between the two groups in this regard (p = 0.257). Blood groups O and B had the highest frequency in the two groups, but the difference was still not significant (p = 0.730). There was no significant difference between the two groups in terms of the need for transfusion (p = 0.471) (Table 5).

**Table 5**: Comparison of blood group and need for blood transfusion between intervention and control groups

| Variable | | Group | | X2 | P value |
|---|---|---|---|---|---|
| | | With Tranexamic acid | Without Tranexamic acid | | |
| RH | + | 34 (81.0%) | 40 (88.9%) | 2.720 | 0.257 |
| | - | 8 (19.0%) | 4 (8.9%) | | |
| ABO | O | 13 (31.0%) | 17 (37.8%) | 2.804 | 0.730 |
| | AB | 7 (16.7%) | 5 (11.1%) | | |
| | B | 8 (19.0%) | 8 (17.8%) | | |
| | A | 13 (31.0%) | 14 (31.1%) | | |
| Need to transfusion | Yes | 5 (11.1%) | 9 (20%) | 1.353 | 0.245 |
| | No | 40 (88.9%) | 36 (80%) | | |

The two study groups were examined for surgical complications, but no significant difference was observed between the two groups (P = 0.103) (Table 6).

**Table 6**: Comparison of surgical complications between intervention and control

| Complication | Control | Intervention | $X^2$ | P value |
|---|---|---|---|---|
| Fever | 9 (56.3%) | 12 (85.7%) | 3.597 | 0.103 |
| Delayed bleeding | 1 (6.3%) | 0 (0%) | | |
| Urinom | 1 (6.3%) | 0 (0%) | | |
| Cellulitis of surgery site | 5 (31.3%) | 2 (0%) | | |
| Clot retention | 2(4.4%) | 4(8.8%) | | |
| Organ injury | 0 | 0 | | |
| Open surgery because of intra-abdominal fluid retention | 1(2.2%) | 1(2.2%) | | |

The two study groups were examined for surgical history, but no significant difference was observed between the two groups, but in the two groups, ESWL cases were among the most surgical history (P <0.05) (Figure 3).

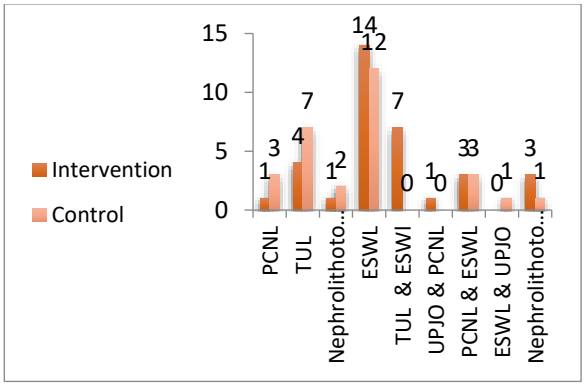



**Figure 3**: Comparison of surgical history between intervention and control groups

## Discussion

In Iran, Tranexamic acid has been used to reduce bleeding and reduce the need for transfusion in urological, cardiac, gynecological and cesarean surgeries, spinal and neurosurgery and orthopedic surgeries (22-30). This study was the first study in PCNL surgery to assess the effect of topical (not injectable) Tranexamic acid for preventing hemoglobin drop after surgery. The results were obtained to confirm the hypothesis of "inequality between the two groups in terms of changes in hemoglobin before and after use of topical Tranexamic acid". In a study conducted by Mohammadi et al 2019 re-evaluate the efficacy of Tranexamic acid in reducing bleeding during PCNL surgery, the intervention group administered 1 gr intravenous Tranexamic acid before induction of anesthesia and then 1 gr Tranexamic acid every 8 hours for two days. The mean decrease in hemoglobin in the Tranexamic acid group was 2.2 gr/dl and in the control group was 2.4 gr/dl, which was not statistically significant (p= 0.312). Regarding bleeding volume, an average of 751 ml was recorded in the Tranexamic acid group and 826 ml in the control group, which was not statistically significant (p=0.416). They concluded that Tranexamic acid was not associated with reduced intraoperative bleeding and had no significant effects and suggested further studies in this field (32). This study was not consistent with the results of our study, which may be related to the method of administration of the drug (injection or topical), as the topical effect of this drug can be more pronounced in this type of surgery.

Consistent with the results of our study, in another study by Mohammadi et al, to investigate the effect of Tranexamic acid in reducing bleeding and hemoglobin loss in patients undergoing PCNL surgery to remove nephrolithiasis, the volume of bleeding in the group receiving Tranexamic acid was significantly lower than the control group. Bleeding volume increased significantly with the duration of surgery. The mean of hemoglobin was 12.5 in the intervention group and 11.47in the control group, which was statistically significant (p <0.001). The final conclusion of the study indicates a reduction in the risk of bleeding in the Tranexamic acid group and also prevents a decrease in hemoglobin after surgery (31).

In the orthopedic department, Abrisham et al conducted a study entitled "Comparison of the effect of topical use of Tranexamic acid versus intramedullary injection on amount of bleeding after knee arthroplasty." The results showed that the hemoglobin level in patients in the placebo injection group was significantly reduced and this decrease was significant. The need for blood transfusion and the rate of anemia in patients after knee arthroplasty compared to placebo was different (33).

In other surgeries, Tranexamic acid has been shown to have beneficial effects in reducing bleeding as well as preventing hemoglobin loss after surgery. Alvadi et al assessed the use of Tranexamic acid in children by 30 mg / kg and infusion of 100 mg / hr. in adults or 1 mg/kg/hr. in children during surgery and 5 hours after surgery. Finally 49% reduction in bleeding and 80% less need for Transfusion was observed which was significantly different compared to the control group with no complications (34).

Another study also obtained the results of our study. Haddadi et al investigated the use of Tranexamic acid to reduce bleeding and the need for transfusion in traumatic mandibular surgery. Patients in the intervention group received intravenous Tranexamic acid 10 mg/kg. Intraoperative bleeding rate, preoperative and postoperatively hemoglobin and hematocrit, need for transfusion and quality of operation field were recorded. The mean bleeding rate in the Tranexamic acid group was much lower than the control group and there was a strong and significant difference. Decreased hemoglobin and hematocrit levels in the Tranexamic acid group 66 hours after surgery were lower than in the control group, and the operation field status and surgeon satisfaction were better in the Tranexamic acid group than in the control group (35).

This study showed the beneficial effects of Tranexamic acid in reducing postoperative bleeding volume and hemoglobin. In our study, the volume of bleeding could not be calculated because patients were given topical Tranexamic acid during drainage and in fact the aim of this study was to evaluate the reduction of hemoglobin after surgery (not during surgery). Considering that at the time of publishing this article, we have experienced an important epidemic in medical history (COVID-19) that has affected all aspects of a human being physically and psychologically, including kidneys, liver, lungs, blood system., etc., therefore, it is recommended to check before taking coagulation factors due to the possibility of interaction of Tranexamic acid with COVID-19 (36-44).

## Conclusion

This study showed that the use of topical Tranexamic acid after the end of PCNL can prevent a decrease in patients' hemoglobin. Topical Tranexamic acid is useful in patients with low preoperative hemoglobin levels, as well as where the length of surgery can be longer or the volume and high number of stones.

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