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Topical versus Intravenous Tranexamic Acid in Reducing Blood Loss during Transurethral Resection of Prostate

Abdallatif M. Aboushawareb, **Hany A. Abdullah, Iman Y. Ismail, Esam Abdelgawad***
Urology Department, Faculty of Medicine, Suez Canal University, Egypt
Corresponding author: Esam Abdelgawad, **Telephone:** +201501599744,
ORCID: 0000-0003-2055-4791, **E-mail:** esam76u@gmail.com

ABSTRACT

Background: Transurethral Resection of Prostate (TURP) is still the first option in treatment for these patients. The main adverse effects of TURP are bleeding and absorption of irrigation fluid.

Objective: The main aim of the current study is to compare the efficacy of topical versus intravenous Tranexamic Acid (TXA) acid in decreasing blood loss in TURP.

Patients and methods: This study was carried out over a period of 9 months on 56 patients presenting with Lower Urinary Tract Symptoms (LUTS) secondary to senile enlarged prostate refractory to medical therapy and to TURP at Urology Department in Damietta Specialized and Suez Canal University Hospitals. Patients were divided into 2 groups; Group A received one gram of TXA intravenously at the beginning of the surgery, while the patients in the Group B received the drug in the irrigation fluid 500 mg/liter. Intraoperative blood loss was measured from the collecting bucket. Vital signs were observed for both groups preoperatively, during and after the surgery. Hemoglobin was determined preoperatively and postoperatively.

Results: Our results found higher reduction in operative blood loss in Group A in comparison to Group B which was 147 and 215 ml, respectively. Moreover, we found that the mean operative time was highly significant different between both groups, longer in Group B (40 minutes) than in Group A (33 minutes). Our study results showed no difference regarding the hospital stay, capsular perforation, bleeding and clot retention.

Conclusion: The use of TXA intravenously is better than its topical administration in decreasing the surgical blood loss during TURP. There is no evidence of reducing rate of post-operative complications between using TXA intravenously and topically TXA.

Keywords: Tranexamic acid, TURP, Blood loss, Clinical trial, Suez Canal University.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a process in which the pathology results in increased number of both stromal and epithelial cells in the area of the prostate around the urethra which is pathologically known as hyperplasia, and not hypertrophy [(1)]. The accurate cause is not well known; however, "reactivation" of embryonic processes is one of the hypotheses that may cause BPH [(2)].

BPH is a common condition that affects elderly men. Recently, many noninvasive and mini-invasive modalities have become popular for the management of men with voiding symptoms; however, TURP is still the first option in treatment for these patients. The main adverse effects of TURP are bleeding and absorption of irrigation fluid. Factors that influence perioperative blood loss include prostate size, weight of tissue resected, operative time, preoperative urine culture, finasteride treatment, use of acetylsalicylic acid, blood pressure, type of anesthesia, and the age of patient [(3-8)].

To minimize the perioperative bleeding, multiple variable approaches have been tried including [(5-7)]: Intravenous estrogens, traction of the catheter, Intra-prostatic vasopressin, Phenol solution and Finasteride use.

The urothelium and urine contain high percentage of plasminogen activators that cause the dissolution of clots. Thus with increasing fibrinolytic activity, postoperative blood loss increases in urine [(9)]. Therefore, administration of antifibrinolytic elements might reduce the amount of postoperative blood loss caused by TURP [(10,11)].

Tranexamic acid (TXA) is derived from the amino acid lysine and, in humans, exerts an activity against fibrinolysis by reversibly binding to plasminogen [(12)]. Recently, many evidence based studies has concluded that TXA is an effective treatment for minimizing blood loss in cardiac, liver and orthopedic surgery [(13, 14)]. Since TXA enter the extra vascular space and stored in tissues, it act by inhibition of tissue fibrinolysis and stabilize blood clots [(15)].

Bleeding during TURP is a dangerous adverse effect. To minimize postoperative blood loss many variable approaches have been tried. One of the approaches was the use of TXA topical or intravenous; however, role of tranexamic acid in decreasing hematuria after TURP wasn't well studied. Thus, the aim of the current study is to compare the safety and efficacy of intravenous versus topical TXA during TURP.

PATIENTS AND METHODS

This clinical trial was conducted among 56 male patients with BPH suffering from Lower Urinary Tract Symptoms (LUTS) refractory to medical treatment and requiring TURP at the Urology Department in Damietta Specialized and Suez Canal University Hospitals.

Inclusion criteria were patients with prostate size range from 30-80 gm., age more than 18 years old, suffering from LUTs, and candidate for TURP and fit for surgery.

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We excluded patients in whom there were bladder diverticulum, large stone bladder, orthopedic disability preventing lithotomy position, allergy to tranexamic acid, and history of thromboembolic disorders.
We divided the included patients into two different groups:

Group A: It included 28 patients who were candidates for TURP who received one gram of TXA (Kapron®, Amoun, Egypt) diluted in 100 ml 5% glucose solution and administered slowly intravenous drip on table.

Group B: It included 28 patients who were candidates for TURP who received TXA in 1.5% glycine irrigation fluid as 500mg/liter.
All patients were subjected to preoperative assessment in form of heart rate and blood pressure measurement before surgery**,** hemoglobin (Hb), hematocrit value levels, coagulation profile, liver enzymes, S. albumin, S. total bilirubin, fasting blood glucose, S. creatinine, and S. urea levels.

Intraoperative Procedures:

In both groups, we used 1.5% glycine as irrigation fluid, which was then calculated and 1000U of heparin was added to it. Sample was collected from irrigant fluid returned to the collecting bucket for Hb. The Hb content of irrigating fluid calculated as prescribed by Shrestha et al. [16].
The following formula was used for measuring intraoperative blood loss:

$$\text{Blood loss in ml} = \frac{\text{Hb content of the irrigants (gm/L)} \times \text{Volume (L)} \times 1000}{\text{Blood Hb (gm/L)} \times 5.2}$$

We used this formula because it is simple, easy and previously used in several studies.

Postoperative care:

Patients were brought to the recovery room immediately post-TURP, and heart rate and blood pressure checked and the Electrolytes and Complete blood counts testes were sent. The patients were monitored and any electrolyte imbalances were corrected. Blood counts are also checked immediately postoperatively, and transfusions are very carefully given, But positive history of coronary or cerebral vascular disease or any ischemic symptoms in patients post TURP, should be transfused promptly and considered for intensive monitoring.

Follow up:

After discharge, patients were instructed about the signs and symptoms of a thromboembolic event. Side effect of the tranexamic acid may be transient, in form of gastro-intestinal symptoms as nausea, vomiting and diarrhea and rarely thromboembolism.

Outcome measures: Estimating blood loss during TURP by special formula was our primary outcome.

Ethical Approval:

The study was approved by the Ethics Board of Suez Canal University and an informed written consent was taken from each participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 20 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Quantitative data were expressed as mean and standard deviation (SD). Chi square test ($\chi 2$) and Fisher's exact test to calculate difference between two or more groups of qualitative variables. Independent samples t-test/ Mann Whitney test was used to compare between two independent groups of quantitative data. Spearman's correlation test was used for non-parametric data. Linear regression analysis was used to study factors affecting duration of TOP in the studied cases P value $\leq$ 0.05 was considered significant.

RESULTS

The participating patients were divided into 2 groups: In group A, ages ranged from 30- 96 years with a mean of 68.89 (SD 9.46 years) and BMI ranged from 18-35 with a mean of 26.61 (SD 3.67). In group B, age ranged from 39-85 years with a mean of 65.96 (SD 8.18) years, and BMI ranged from 15-33 with a mean of 25.43 (SD 3.85). No significant differences were found between age and BMI of the 2 studied groups (P values 0.233 and 0.225, respectively).

There was no significant difference between both groups regarding the complaint, comorbidities, surgical history, IPSS score, pre-operative Hb, prostate size by DRE and presence of indwelling urethral catheter (Table 1).

Table (1): Comparison between the 2 studies groups regarding the preoperative assessment.

Variable		Groups				P value
		Group A		Group B		
		Count (N)	Percent (%)	Count (N)	Percent (%)	
Complaint	**Hematuria**	2	7.1%	3	10.7%	0.695*
	LUTS	20	71.4%	17	60.7%	
	Retention	6	21.4%	8	28.6%	
Comorbidities	**NIL**	17	60.7%	15	53.6%	0.85 *
	DM	9	32.1%	11	39.3%	
	CLD	2	7.1%	2	7.1%	
Surgical Urological H.	**No**	23	82.1%	25	89.3%	0.445**
	Yes	5	17.9%	3	10.7%	
Prostate size by DRE	**+1**	2	7.1%	1	3.6%	0.815*
	+2	20	71.4%	20	71.4%	
	+3	6	21.4%	7	25.0%	
Indwelling urethral catheter	**No**	20	71.4%	20	71.4%	0.99**
	Yes	8	28.6%	8	28.6%	
Quantitative Variables		Mean	Standard Deviation	Mean	Standard Deviation	
Pre-operative Hb		12.36	1.49	12.40	1.24	0.787***
IPSS		25.71	3.87	25.14	3.75	0.575***

*Chi square test. **Fischer's Exact test. *** Mann Whitney test.

There was a significant difference among the two groups regarding Hb drop, Hb in irrigant, irrigant volume and operative time. As the p. value was highly significant; this means that the Hb drop and operative time in *Group A* were lower than *Group B*. This means that the blood loss with intravenous TXA was lower than that with topical instillation (Table 2).

Table (2): The intraoperative parameters in both groups.

Variable	Groups				P value
	Group A		Group B		
	Mean	Standard Deviation	Mean	Standard Deviation	
Drop in Hb	0.98	0.37	1.25	0.38	0.008
Irrigant Hb	0.88	0.26	1.05	0.31	0.020
Irrigant volume(L)	9.32	2.61	11.11	2.23	0.002
Operative time(min)	33.04	12.79	40.07	11.10	0.009

Mann Whitney test

There was no significant difference among the two groups regarding the resected prostatic tissue, the hospital stay and blood transfusion units (Table 3).

Table (3): The difference in resected prostatic tissue volume, hospital stay, blood transfusion units in both groups.

Variable	Groups				P value
	Group A		Group B		
	Mean	Standard Deviation	Mean	Standard Deviation	
Resected prostatic tissue volume	21.36	6.11	21.71	5.67	0.869
Hospital stay	2.04	0.19	2.04	0.19	0.98
Blood transfusion units	0.04	0.19	0.18	00.67	0.529

MannWhitney test

There was no significant difference between both groups regarding perforation, bleeding and clot retention. There were no reported cases of DVT, post-operative sepsis or TUR syndrome (Table 4).

Table (4): The complications rate in both groups.

Complications	Groups				P value
	Group A		Group B		
	Count	Column N %	Count	Column N %	
NIL	23	82.1%	18	64.3%	0.124
Perforation	1.0	3.6%	0.0	0.0%	
Bleeding and clot retention	4.0	14.3%	10	35.7%	

Chi square test

In group A. There was positive correlation among Prostate size by DRE and Total blood loss, Prostate size by US, irrigant volume and operative time. And this means that with the increase in prostate size by DRE, the Total blood loss, Prostate size by US, irrigant volume and the operative time increase.

There was positive correlation between Prostate size by US and Prostate size by DRE, Total blood loss, irrigant volume, operative time and resected tissue volume. And this means that with the increase in prostate size by US, the Total blood loss, irrigant volume, operative time and resected tissue volume increase (table 5).

Table (5): the correlations between prostate size by DRE and US and the other parameters in group A.

Group			Prostate size by DRE	Indewelling urethral catheter	Pre operative Hb	Post operative Hb	Drop in Hb	Total blood loss	Prostate size by US	Irrigant Hb	irrigant volume	operative time	resected tissue volume	hospital stay	Complications	Blood Transfusion units
Group A	Prostate size by DRE	Pearson Correlation	----	.439	-.277	-.305	.109	.476	.725	.073	.614	.623	.284	.320	.141	.320
		Sig. (2-tailed)		.020	.154	.114	.580	.011	.000	.713	.001	.000	.143	.097	.473	.097
		N		28	28	28	28	28	28	28	28	28	28	28	28	28
	Prostate size by US	Pearson Correlation	.725	.190	-.218	-.218	-.003	.494	1	.079	.671	.691	.660	.417	.108	.417
		Sig. (2-tailed)	.000	.334	.266	.265	.989	.008		.690	.000	.000	.000	.027	.583	.027
		N	28	28	28	28	28	28	28	28	28	28	28	28	28	28

In group B, There was positive correlation between Prostate size by DRE and Prostate size by US and resected tissue volume. And this means that with the increase in prostate size by DRE, the Prostate size by US and resected tissue volume increase.

There was positive correlation between Prostate size by US and Drop in Hb, total blood loss, operative time, resected tissue volume, Prostate size by DRE and irrigant Hb. This means that with the increase in prostate size by US, the Drop in Hb, Total blood loss, operative time, resected tissue volume, Prostate size by DRE and irrigant Hb increase (table 6).

Table (6): The correlations between prostate size by DRE and US and the other parameters in Group B.

Group			Prostate size by DRE	Indewelling urethral catheter	Pre operative Hb	Post operative Hb	Drop in Hb	Total blood loss	Prostate size by US	Irrigant Hb	irrigant volume	operative time	resected tissue volume	hospital stay	Complications	Blood Transfusion units
Group B	Prostate size by DRE	Pearson Correlation	----	.208	.227	.172	.160	.225	.790	.265	.078	.345	.402	.309	.130	.214
		Sig. (2-tailed)		.289	.246	.382	.415	.250	.000	.173	.692	.072	.034	.110	.508	.274
		N		28	28	28	28	28	28	28	28	28	28	28	28	28
	Prostate size by US	Pearson Correlation	.790	.241	.089	-.050	.397	.376	1	.432	.077	.383	.495	.345	.214	.282
		Sig. (2-tailed)	.000	.216	.651	.801	.037	.049		.022	.699	.044	.007	.072	.274	.145
		N	28	28	28	28	28	28	28	28	28	28	28	28	28	28

Multivariate analysis in Group A as regarding total blood loss, the BMI was a positive predictor. This means that as BMI increase the total blood loss increase. Age, IPSS, Prostate size by DRE and Prostate size by US were not predictors of total blood loss in group A.
Multivariate analysis in Group B as regarding total blood loss, the age was a positive predictor.

This means that as age increase the total blood loss increase. BMI, IPSS, Prostate size by DRE and Prostate size by US were not predictors of total loss of blood in group B.

Table (7): Predictors of Total Blood Loss in both groups.

Group	Model	Coefficients	P value
Group A	age	-1.334	0.471
	BMI	10.610	0.033
	IPSS	1.788	0.684
	Prostate size by DRE	53.716	0.268
	Prostate size by US	1.397	0.518
Group B	age	7.202	0.006
	BMI	4.329	0.425
	IPSS	4.650	0.410
	Prostate size by DRE	17.041	0.796
	Prostate size by US	2.879	0.249

Multivariate analysis in Group A as regarding operative time, the IPSS was a positive predictor. This means that as IPSS increase the operative time increase. Age, BMI, Prostate size by DRE and Prostate size by US were not predictors of operative time in Group A.

Multivariate analysis in Group B as regarding operative time, the age, BMI, IPSS, Prostate size by DRE and Prostate size by US were not predictors of operative time in Group B.

Multivariate analysis in Group A as regarding hospital stay, BMI was a positive predictor. This means that as BMI increase the hospital stay increase. Age, IPSS, Prostate size by DRE and Prostate size by US were not predictors of hospital stay in Group A.

Multivariate analysis in Group B as regarding hospital stay, Age was a positive predictor. This means that as age increase the hospital stay increase. BMI, IPSS, Prostate size by DRE and Prostate size by US were not predictors of hospital stay in Group B.

Multivariate analysis in Group A as regarding blood transfusion, BMI was a positive predictor. This means that as BMI increase the blood transfusion rate increase. Age, IPSS, Prostate size by DRE and Prostate size by US were not predictors for blood transfusion in Group A.

Multivariate analysis in Group B as regarding blood transfusion, Age, BMI, IPSS, Prostate size by DRE and Prostate size by US were not predictors of blood transfusion in Group B.

Table (8): Predictors of blood transfusion in both groups.

Group	Model	Coefficients	P value
Group A	Age	-0.005	0.220
	BMI	0.022	0.030
	IPSS	-0.004	0.674
	Prostate size by DRE	0.003	0.979
	Prostate size by US	0.005	0.248
Group B	Age	0.032	0.052
	BMI	0.032	0.369
	IPSS	0.022	0.557
	Prostate size by DRE	0.264	0.542
	Prostate size by US	0.005	0.745

DISCUSSION

Benign prostatic enlargement is a condition affecting many elderly people. Recently, many modalities have been tried for the management of men with voiding LUTs; however, TURP is still the main therapy for management of these patients with bothersome symptoms. The main adverse effects of TURP are bleeding and absorption of the irrigation fluid. Factors that affect perioperative loss of blood, include prostate size, weight of the tissue resected, operative time and patient age [3-8]. TXA was shown to significantly reduce the complications due to bleeding without affecting the veno-occlusive events [17].

Patients in both groups were matched regarding age, BMI, complaint, comorbidities, surgical history, IPSS score, pre-operative Hb, prostate size by DRE and presence of indwelling urethral catheter, which indicate that the two groups were comparable.

In the present study there was extremely significant difference between both groups regarding the mean total loss of blood that was (**147**ml) in group A where we use TXA intravenously and (**215** ml) in group B where we used the drug locally, (P <0.001)., which is similar to Rannikko et al who found that the median amounts of total blood loss in the TXA and control group were (**128** and **250** mL, P= 0.018), respectively after receiving 2 g TXA orally three times daily on the day of surgery and first postoperative day [18].

This was the same as that for Pourfakhr et al. [19], who reported that the topical administration of TXA (500 mg TXA with 5 mL total volume) post prostatectomy considerably reduced blood loss and with Samir et al. [20] who stated that high-dose TXA was highly efficient in controlling blood loss during bipolar TURP in patients with large prostates. On the other hand, Moharam zadeh et al. [17], stated that there was no considerable effect of the local use of TXA on blood loss.

We found that the mean drop in Hb was highly significant in the group using TXA intravenously than the group using it locally which was **0.98** and **1.25** respectively (P= 0.008), which was similar to Abdullah et al. who found that the mean drop in Hb in the TXA and control group were **0.87** and **0.98**, respectively after receiving irrigation fluid with 500 mg tranexamic acid in one liter of normal saline and placebo [22,17].

We found that the mean operative time was considerably different between both groups, longer in Group B (**40 min**) than in Group A **(33 min**), (P= 0.009), which was similar to Rannikko et al. [18] who found that tranexamic acid treatment reduced the duration of operation (median **36 minutes** versus **48 minutes**, *P* <0.001) and Abdullah et al. who found the mean resection time (**36.53** vs **31.46**) after using TXA locally [22].

In our study there was considerable difference regarding the mean volume of irrigation fluid used which was lower in Group A (**9.3** L) than in Group B (**11.1** L), (P= 0.002)., which was similar to Rannikko et al. who reported that the amount of irrigating fluid used (median **15** L versus **18** L, *P* = 0.004) [22].

The decrease in blood loss during TURP as a result of TXA mostly led to improved visibility that shortened the duration of operation and lower volume of intraoperative irrigation fluid. The is associated fear of usage of TXA inducing thromboembolic events, although No one of the participants in older studies and in our prospective randomized study had symptomatic deep vein thrombosis, myocardial infarction or pulmonary embolism.

There was no significant difference among the two groups concerning the hospital stay which was 2 days (P= 0.98), which was similar to Rannikko et al. who reported that hospital stay in the group using TXA was 3 days which was not different from the other group (P= 0.218) [18].

Regarding the complications in our study, there was no considerable difference between the two groups concerning bleeding, clot retention and capsular perforation.

On regression analysis the most important factors that affect total blood loss were BMI in Group A, and none in Group B.

Lack of control group was one of the limitations of this study. Although this study did not reach definite conclusions about the long term safety of TXA, there is no sufficient evidence in the existing literatures about the long term safety of TXA.

In conclusion, the use of TXA intravenously is better than its topical administration in decreasing the surgical blood loss during TURP. There is no evidence of reducing rate of post-operative complications between using TXA intravenously and topically.

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