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Preventing Excessive Blood Loss During Percutaneous Nephrolithotomy by Using Tranexamic Acid: A Double Blinded Prospective Randomized Controlled Trial

Traneksamik Asidi Kullanarak Perkütan Nefrolitotomi Sırasında Aşırı Kan Kaybını Önleme: Çift Körü Körüne Prospektif Rastgele Kontrollü Deneme

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What's known on the subject? and What does the study add?

Percutaneous nephrolithotomy is most frequently performed procedure for renal stones measuring 2 cm. Perioperative hemorrhage being most common complication, warrants as important predicting factor of adverse outcomes. Prevention with inexpensive safe drug like Tranexamic acid would ultimately turn out to be cornerstone for establishing future guidelines. Currently there is only one study published internationally highlighting this notion. Therefore this study will be beneficial for researchers in shaping the current practices.

Abstract

Objective: Percutaneous nephrolithotomy (PCNL) is most frequently performed procedure for renal stones 2 cm and larger. Perioperative hemorrhage being most common complication, warrants as important predicting factor of adverse outcomes. Prevention with inexpensive and safe drug like tranexamic acid (TA) would ultimately turn out to be cornerstone for establishing future guidelines. Aim of this study is to evaluate whether TA is efficacious in preventing blood loss during PCNL.

Materials and Methods: Ethical review board approval taken. Sample size calculation yielded 240 patients, comprising 120 in each group. Group A receiving TA and group B receiving placebo. Age, gender, body mass index (BMI), stone size, volume and location, preoperative blood count, creatinine, urine analysis, coagulation profile and necessary radiological investigations done. Randomization through lottery method. Both patient and investigator were blinded. Hemoglobin (Hb) and hematocrit (Hct) levels done at 24 hours postoperatively and fall in values recorded.

Results: Both groups were equal in characteristics like age, gender, BMI, stone size, volume and location ($p>0.05$). Operative variables like calyx punctured, position of puncture and operative time were also found to be similar in both groups. Median change in Hb in placebo group was 1.6 interquartile range (IQR) 4, while in TA group was 1.3 (IQR 7.8) ($p=0.001$). Similarly, median change in Hct level in placebo group was 3.6 (IQR 11.8) and in TA group was 2.4 (IQR 13) ($p<0.001$). Sixteen patients were transfused after surgery; 12 (75%) belonged to placebo group while 4 (25%) belonged to TA group ($p=0.038$). Hospital stay was not significantly different in both groups ($p=0.177$) with median of 4.0 and IQR of 0 in both groups.

Conclusion: TA during PCNL reduces blood loss and minimizes blood transfusion rate.

Keywords: Tranexamic acid, percutaneous nephrolithotomy, bleeding, blood transfusion

Öz

Amaç: Perkütan nefrolitotomi (PNL), 2 cm ve daha büyük böbrek taşları için en sık uygulanan prosedürdür. Perioperatif kanama en yaygın komplikasyon olup, istenmeyen sonuçların öngörülen önemli faktörüdür. Traneksamik asit (TA) gibi ucuz ve güvenli ilaçlarla önleme, nihayetinde gelecek kılavuz ilkeleri oluşturmak için temel taş haline dönüşebilir. Bu çalışmanın amacı, TA'nın PNL sırasında kan kaybını önlemede etkili olup olmadığını değerlendirmektir.

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Gereç ve Yöntem: Etik kurulun onayı alındı. Örneklem boyutu hesaplamasında, her bir grupta 120'den oluşan 240 hasta oluşturulmuştur. Grup A, TA ve grup B'yi alan plasebo. Yaş, cinsiyet, vücut kitle indeksi (VKİ), taş boyutu, hacim ve yer, preoperatif kan sayımı, kreatinin, idrar analizi, pıhtılaşma profili ve gerekli radyolojik tetkikler yapıldı. Piyango yöntemi ile rastgele oluşturma. Hem hasta hem de araştırmacı kör oldu. Postoperatif 24 saat yapılan hemoglobin (Hb) ve hematokrit (Hct) düzeyleri ve düşen değerler kaydedildi.
Bulgular: Her iki grup yaş, cinsiyet, VKİ, taş boyutu, hacim ve yer gibi özelliklerde eşitti (p>0,05). Her iki grupta da, kaliks ponksiyonu, ponksiyon yeri ve operasyon süresi gibi operatif değişkenlerin benzer olduğu bulundu. Plasebo grubunda Hb'de medyan değişim 1,6 [çeyrekler arası aralık (IQR) 4] iken, TA grubunda 1,3 (IQR 7,8) idi (p=0,001). Benzer şekilde, plasebo grubundaki Hct düzeyindeki medyan değişim 3,6 (IQR 11,8) ve TA grubunda 2,4 (IQR 13) idi (p<0,001). Ameliyat sonrası 16 hasta transfüze edildi; 12 (%75) plasebo grubuna, 4 (%25) TA grubuna (p=0,038) aitti. Her iki grupta da ortalama 4,0 ve IQR 0 olan hastanede kalış süresi iki grup arasında anlamlı farklılık göstermedi (p=0,177).
Sonuç: PNL sırasında TA kan kaybını azaltır ve kan transfüzyon hızını en aza indirir.
Anahtar Kelimeler: Traneksamik asit, perkütan nefrolitotomi, kanama, kan transfüzyonu

Introduction

Percutaneous nephrolithotomy (PCNL) is the standard of care for the management of large upper urinary tract calculi because of its higher stone clearance and cost-effectiveness when compared with other treatment alternatives such as extracorporeal shockwave lithotripsy and flexible ureteroscopy (1). Although the safety of PCNL has been established from various studies and resources (2), there is still compelling evidence that hemorrhage is one of the commonest complications of PCNL. The source of bleeding during or after PCNL is usually the segmental arteries, and is mostly controlled by conservative measures (3). Failure to identify a bleeding arterio-venous fistula or a pseudo aneurysm may result in catastrophe and may alter the disease outcome (4). Such cases may require angiographic embolization for the cessation of bleeding (5). Hemorrhages that require embolization are between 0.3% and 1.4% (4,6). This angiographic embolization can be selective or highly selective, depending on the level and degree of hemorrhage (7). Another dilemma about the outcome of hemorrhage after PCNL is that there is no fixed consensus about the management of hemorrhage post PCNL (5,8). The inference from different studies suggests that the blood transfusion rate for hemorrhage post PCNL ranges between 3 to 23% (4,6,9).

In urological surgeries, postoperative blood loss is thought to be associated with an increase in urinary fibrinolytic activity. Urine and urothelium contain high concentrations of plasminogen activators that facilitate the lysis of clots (10). Therefore, administration of antifibrinolytic agents might be beneficial in reducing the amount of postoperative blood loss resulting from these urological surgeries (11,12). Taking these facts in to consideration, there have been various measures undertaken to prevent or control hemorrhage during PCNL. One of these is the use of tranexamic acid (TA) which is a synthetic derivative of amino acid lysine and has an antifibrinolytic activity by reversibly binding to plasminogen (13). TA is ten times more potent in binding to plasminogen than aminocaproic acid which is a derivative and analogue of amino acid lysine and has been used historically for perioperative and postoperative bleeding control, but with conflicting results (14,15,16). TA accumulates in the extracellular space of tissues where it exerts its antifibrinolytic action. The consequent stabilization of the blood clots is not associated with laboratory signs of excessive fibrinolysis in the clots (17). Presence of dissoluble blood clots has not been reported in patients receiving TA in different urological surgeries, which would have hampered the vision of surgeon (18). Moreover, the safety of TA has been reported in several studies which clearly negates its thromboembolic outcomes (19,20,21).

Therefore preventing this complication with a safe and inexpensive drug like TA would ultimately turn out to be a cornerstone for establishing future guidelines for PCNL. Furthermore, lack of national and international data on use of TA in this particular urological surgery highlights the need for the above mentioned notion. There is only one study performed internationally by Kumar et al. (22). Other than that, there are 2 reviews by other authors pertaining to the same study. Fenner (23) in 2013, has commented on the study of Kumar et al. (22) and has re-emphasized the use of TA in selected group of patients in whom prolonged operative time is anticipated. Ritter and Michel (24) has also commented on the study of Kumar et al. (22) in 2013 with similar remarks but pointed out few pitfalls in the study like the confounding factors for perioperative and postoperative bleeding which were never discussed in the study and that type and technique of puncture which is a very important predictor of intraoperative hemorrhage, was also never discussed.

Materials and Methods

This double blind randomized controlled trial was conducted at the Kidney Centre Postgraduate Training Institute, Karachi, Pakistan from 7th October 2015 to 1st April 2016 (on completion of sample size). The Kidney Centre Ethical Review Committee approval was taken prior to the study (approval number: 20-URO-022015, date: February 2015). Using sample size calculator, PASS version 11, primary investigator applied 2-proportion formula with 95% confidence interval and 80% power of test to yield a sample size of 240, consisting of 2 equal groups of 120 subjects of group A (TA) and group B (placebo), taking in to account the efficacy of TA to prevent bleeding as 98%, and of placebo as 89%. The reference for variables was taken from a similar previous study (22) in which the TA group had 2% patients needing blood transfusion, in contrast to 11% of patients in control group. All patients aged 16–75 years of both genders, undergoing PCNL for renal stone size of more than 2 cm on ultrasound and X-ray kidney, ureter, and bladder (KUB) or 1 to 2 cm if stone refractory to lithotripsy, were considered for study after informed consent. Non-anemic patients with baseline hemoglobin (Hb) levels of above 12 gm/dL were enrolled. Patients excluded from the study were those with known bleeding disorder (e.g. hemophilia), deranged coagulation profile in preoperative lab workup, serum creatinine greater than 1.5 mg/dL, patients on aminosalicylic acid, clopidogrel or other blood thinning products and patients giving history of hypersensitivity to TA. Informed consent was taken from the patient by primary investigator. Age, gender, body mass index (BMI), stone size, stone volume and stone location were recorded in all patients. Preoperative complete blood count, creatinine, urine analysis, coagulation profile partial thromboplastin, activated partial thromboplastin time and necessary radiological investigations [X-ray KUB, ultrasound KUB, computed tomography (CT) pyelogram etc.] were done in all cases. The ampules of TA and placebo were similar in appearance but were differently coded by a person other than the primary investigator. Randomization for the allocation of subject patients into each group underwent through lottery method by the operating room holding bay staff, to which both the subject (patient) and the investigator (surgeon) were blinded (double blinding). Allocated patient were administered injection TA 1 gm or placebo by the recovery bay staff, before the patient was taken to the operating table. PCNL was performed and all necessary data (like renal calyx punctured and position of puncture) ware recorded. Surgery was carried out by consultant urologist with minimum experience of 10 years. Most frequent modality for positioning the patient for PCNL in our center is the prone position and all of the cases performed for this study were in the same position. The preferred puncture access was performed under fluoroscopic guidance and the technique was either "triangulation" (parallax) or the "bull's-eye" (eye of the needle), depending upon the preference of surgeon. Tract dilatation was performed in all cases with help of Alken's metallic telescoping dilators starting from 9 to 27 French in all patients. A 30 French Amplatz sheath then placed over Alken's dilators to gain access in to renal calyceal system. This was followed by introducing the nephroscope and fragmenting renal stone with pneumatic lithotripter. The fragmented stones were then removed using forceps. Stone clearance was checked on table using the fluoroscope, as well as on first postoperative day using X-ray KUB. Use of a drainage tube (nephrostomy tube) was dependent on duration of surgery, in order to avoid perinephric collection of irrigation fluid, and this nephrostomy tube was usually removed on the first or second postoperative day.

Hb and Hct levels were done at the end of 24 hours postoperatively and fall in values was recorded for calculating efficacy for bleeding control among both arms. The impact of stone size, duration of procedure and blood transfusion rate were also compared between patients of both arms.

Statistical Analysis

Decoding of ampules was performed at the end of all data collection by same assistant who performed coding of ampules in the beginning. Data analysis performed by IBM SPSS version 21. Descriptive analyses of variables presented in terms of frequencies and percentages. Mean and standard deviation computed for normal continuous variables while median with interquartile range (IQR) was used for skewed continuous variables. Normality of data checked by Shapiro-Wilk test. To observe difference between two groups, t-test was applied for normally distributed continuous variables, while Mann-Whitney test was used for asymmetric continuous variables. To detect association between two categorical variables, chi-square test was executed with level of significance as ≤0.05 (p value).

Results

The study incorporated total of 240 participants, 120 in each arms. Both placebo and TA groups were equal in their baseline characteristics (p>0.05) like age, gender, BMI, stone size, stone volume and stone location (Table 1).

Operative characteristics like renal calyx punctured, position of puncture and operative times were also compared between the two groups with no resultant significant difference (Table 1).

Table 1. Demographic, clinical and operative characteristics

Variables		Type of drug		p
		Placebo n=120	Tranexamic acid n=120	
Age (median with IQR)		40, 22	41, 22	0.80
Gender Male (n with %)		82 (68.3%)	72 (60%)	0.18
Female (n with %)		38 (31.7%)	48 (40%)	
BMI (kg/m^2) (median with IQR)		26.17, 8.25	25.73, 7.47	0.23
Stone size (cm) (median with IQR)		2.9, 1.60	2.55, 1.50	0.74
Stone volume (cm^3) (median with IQR)		3.18, 4.90	2.15, 4.53	0.74
Stone location	Multiple calyces (n)	14	15	0.98
	Upper calyx (n)	26	24	
	Pelvis (n)	31	30	
	Lower calyx (n)	49	51	
Operative parameters				
Renal calyx punctured	Upper calyx	57	59	0.44
	Lower calyx	63	61	
Position of puncture	Supracostal	57	54	0.39
	Infracostal	63	66	
Operative time in minutes (median with IQR)		90, 55	85, 30	0.24
Dilators size	20 Fr (<2 cm stones)	11	13	0.41
	30 Fr (>2 cm stones)	109	107	

IQR: Interquartile range, BMI: Body mass index, Fr: French

Table 2. Preoperative and postoperative laboratory parameters of patients receiving tranexamic acid and placebo

Clinical variables	Type of drug		p
	Placebo (n=120)	TA (n=120)	
Preoperative Hb (gm/dL) (median with IQR)	14, 7.7	13.35, 9.1	0.015
Postoperative Hb (gm/dL) (mean ± SD)	12±1.78	11.8±1.8	0.446
Change in Hb (median with IQR)	1.6, 4	1.3, 7.8	**0.001**
Preoperative Hct (%) (mean ± SD)	39.8±4.6	38.6±4.9	0.048
Postoperative Hct (%) (mean ± SD)	36±4.5	35.6±4.8	0.578
Change in Hct (median with IQR)	3.6, 11.8	2.4, 13	**<0.001**

TA: Tranexamic acid, Hb: Hemoglobin, Hct: Hematocrit, SD: Standard deviation, IQR: Interquartile range

Laboratory variables like pre-operative Hb and pre-operative Hct level were statistically different in both groups (p<0.05). Median pre-operative Hb in placebo group was 14 (IQR 7.7) while in TA receiving group was 13.35 (IQR 9.1). Similarly mean pre-operative Hct was also high in in placebo group (39.8±4.6) as compared to TA group (38.6±4.9). To overcome this problem we observed the changes in both Hb and Hct dropped differently in placebo and TA groups. Median of change in Hb levels in placebo group was 1.6 (IQR 4), while in TA group was 1.3 (IQR 7.8) (p=0.001). Similarly, median of change in Hct levels in placebo group was 3.6 (IQR 11.8) and in TA group was 2.4 (IQR 13) (p<0.001) (Table 2).

Total number of patients needing blood transfusion after surgery was 16, among whom 12 (75%) belonged to placebo group while only 4 (25%) belonged to TA group (p=0.038) (Table 3).

The hospital stay was not significantly different in both groups (p=0.177) with median of 4.0 and IQR of 0 in both groups (Table 3).

Table 3. Blood transfusion and hospital stay in both groups

		Type of drug		Total	p
		Placebo n=120	TA n=120		
Blood transfusion	No (n %)	108, 48.2	116, 51.8	224	0.038
	Yes (n %)	12, 75	4, 25	16	
Hospital stay in days (median, IQR)		4.0, 0	4.0, 0		0.177

TA: Tranexamic acid, IQR: Interquartile ratio

Discussion

The present study supports the hypothesis with expectant results and further asserts the need for considering alternative and simple means to minimize blood loss during PCNL. The study also emphasizes on technical aspects of PCNL to minimize confounders for blood loss in similar future studies. We hope to stimulate a notion in the minds of researchers to ponder upon possibilities of non-surgical and inexpensive means of controlling excessive hemorrhage during one of the commonest and traumatic surgical procedures in urology.

The notion of performing this study was based on few concrete observations from literature search which will be discussed sequentially in this section. Only one published international study was found during our study duration which was performed by Kumar et al. (22), which had a sample size of 200 patients (100 in each arm). In view of that, we took an ample sample size (240) which correlated with the frequency of PCNL cases in our center. Secondly, the study by Kumar et al. (22) inadequately mentioned some very important intraoperative details like stone location and volume, puncture technique, calyx punctured and position of puncture, type and size of dilators along with Amplatz size. We feel that these details hold utmost importance because these are vital confounders and affect the results of study.

Many urological surgeries have reaped their benefit of reduced intra and postoperative hemorrhage with the use of TA. Radical cystectomy is one of the bloodiest surgeries when vascular anatomy is taken in to perspective. Pelvic area is considered to be highly vascular and is very prone to bleeding. On top of that, malignancy causes increased angiogenesis which in turn increases the chances of intra and postoperative hemorrhage. A retrospective review stated that patients who underwent open radical cystectomy had less frequent need for perioperative blood transfusion when they were given intravenous TA (25).

A very recent study from North India by Bansal and Arora (26) proposes through randomized controlled trial that TA reduces blood loss during PCNL and also diminishes need for blood transfusion with additional benefits of shorter operative time and hospital stay. But in this study, TA was used in irrigation fluid rather than intravenous administration which resulted in fall in Hb and total blood loss in Tranexamic group to be significantly lower than placebo group (1.71 vs. 2.67 gm/dL, 154.55 vs. 212.61 mL, respectively ($p<0.0001$).

Similarly, use of TA in lowering blood loss and need for transfusion has been documented in various published studies pertaining to Obstetrics/Gynecology, Orthopedics, Head and Neck and Cardiac surgery (27,28,29,30).

Study Limitations

Few limitations in our study are worth mentioning for future researchers to take in to account. Some patients (24 out of 240) underwent tract dilatation up to 18 French and subsequent Amplatz size of 20 French. These were the cases where stone size was less than 2 cm. This was probably a limitation of the study but since both arms contained similar number of such patients (11 in placebo and 13 in TA group) ($p=0.41$), this limitation would not become a source of large and significant bias. Hounsfield unit calculation of stone on a CT scan which gives a good estimation of degree of hardness of a stone, could not be calculated in our study due to lack of necessary software in the CT scan console. This is yet another limitation of the study which could have effects on operative times and subsequent blood loss. Another limitation of the study is that the dose of TA was constant (1 gm) in all the patients, despite the weight of patient to whom it was administered. Food and drug administration approved drug dosage literature only suggests a single perioperative dose of 10 mg/kg in hemophilia patients undergoing tooth extraction, whereas no patient in in our study received a dose less than this suggested dosage.

Conclusion

It can be concluded with great confidence that an inexpensive and relatively safe drug like TA is highly efficacious in preventing excessive blood loss during a traumatic surgery like PCNL. We can also conclude that TA not only makes surgery easy and operative time short, but also minimizes the need for blood transfusions during PCNL. Despite that fact, further similar prospective trials are needed to strengthen the level of evidence for guidelines on the use of this drug and to evaluate the demographical variation in the results of its use.

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Primary investigator, patients or helper nurses in holding bay didn't have any conflict of interest. Drug TA was provided free of cost by Hilton Pharma (PVT) Ltd. without demand of any favor in return.

Ethics

Ethics Committee Approval: This study was approved by the Kidney Centre Ethical Review Committee (approval number: 20-URO-022015, date: February 2015).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.S., S.K., Concept: A.S., Design: A.S., Data Collection or Processing: S.A., I.S., J.S., Analysis or Interpretation: H.M., Literature Search: A.S., Writing: A.S., S.K.

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