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Desmopressin Acetate in Percutaneous Ultrasound-Guided Native Kidney Biopsy in Patients with Reduced Kidney Function: A Double-Blind Randomized Controlled Trial

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Original Paper

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Keywords. kidney disease, biopsy, complication, bleeding, hematoma, hematuria, desmopressin, clinical trial

Introduction. Bleeding events are the most common complications after kidney biopsy. This study aims to evaluate the effect of desmopressin administration on bleeding complication, in native kidney biopsy candidates with reduced kidney function.

Methods. This double-blind randomized clinical trial enrolled 18 to 80 years old patients with 15 < eGFR < 90 mL/min/ 1.73m² from July 2017 to August 2020. Patients were randomly assigned to receive either 3 µg/kg of intranasal desmopressin acetate or 1 mL/kg of intranasal sodium chloride 0.65%, one hour before ultrasound-guided, percutaneous native kidney biopsy. The primary outcome was the post-biopsy bleeding complications, and secondary outcomes were the volume of perirenal hematoma, and changes of post-biopsy hemoglobin and hematocrit level, plasma sodium and blood pressure (Clinical Trial Registration ID: IRCT20090701002112N3).

Results. A total of 120 patients (58 men and 62 women), 60 patients in each group, were analyzed. The mean age and eGFR of the patients were 45.29 ± 15.95 years and 51.77 ± 18.02 ml/min/ 1.73m², respectively. Desmopressin administration significantly decreased post-biopsy perirenal hematoma compared to placebo (7/60 [11.6%]) vs. 33/60 [40%]; $P < .05$), and the hematoma volume was significantly smaller in the desmopressin group, in case of hematoma formation (2.31 ± 1.17 vs. 7.72 ± 5.45 mm³, $P < .05$).

Conclusion. Desmopressin administration before kidney biopsy is a safe and effective strategy to prevent bleeding complications. Considering absolute risk reduction of about 28%, the number needed to treat is about 4 procedures. We recommend considering desmopressin administration before percutaneous native kidney biopsy.

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INTRODUCTION

Kidney biopsy is the gold standard procedure for the diagnosis, of patients, suffering from kidney diseases. Although technical advances such as real-time ultrasound guidance and automated gun needles have improved the accuracy and safety of kidney biopsy, the procedure is not risk-free.[1-6] One of the most common complications following kidney biopsy is bleeding, including hematoma (11.6%), gross hematuria (3.5%), need

for blood transfusion (0.9-1.6%) and angiographic intervention (0.3 to 0.6%), nephrectomy (0.01%), bladder obstruction (0.3%), and death (0.02%).[7-9]

The pathophysiology of the bleeding tendency in patients with kidney disease is multifactorial and includes, decreased platelet aggregation and abnormal platelet-endothelial adhesion, which is partially due to impaired platelet-von Willebrand factor (VWF) interaction.[10-16] Numbers of therapeutic options such as dialysis, packed red cell transfusion, estrogen, cryoprecipitate, and desmopressin acetate have been proposed to improve platelet function and reduce bleeding risk.[17-27] Desmopressin acetate, also known as 1-deamino-8-D-arginine vasopressin (DDAVP), is a synthetic analogue of the antidiuretic hormone, vasopressin, which has been shown to be effective in various inherited and acquired bleeding conditions such as von Willebrand disease type I, hemophilia, chronic liver disease, and uremia. The hemostatic effect of desmopressin is mediated by endothelial-vasopressin receptor II, through which the VWF and factor VIII levels increase in circulation.[25-29]

To date, only one randomized controlled trial has showed the efficacy of desmopressin acetate in decreasing kidney biopsy-related bleeding complications, in patients with estimated glomerular filtration rate (eGFR) > 60 mL/min/ 1.73m^2,[30] and level one evidence regarding the effect of desmopressin on bleeding complications, following ultrasound-guided percutaneous native kidney biopsy, in patients with declined eGFR, especially < 60 mL/min/ 1.73m^2, is lacking.[5,6,31] Therefore, this trial seeks to bridge this gap. We hypothesized that desmopressin administration, before kidney biopsy, decreases the bleeding complications.

MATERIALS AND METHODS

Study Overview

This randomized, double-blind clinical trial was conducted from July 2017 to August 2020, on ultrasound-guided percutaneous native kidney biopsy candidates, at the two tertiary care referral centers, Golestan and Imam Khomeini hospitals, which are affiliated to Ahvaz Jundishapur University of Medical Sciences (AJUMS), Ahvaz, Khuzestan, Iran. The ethics committee and the institutional review board of AJUMS approved the study protocol and informed consents of the patients (Reference Number: IR.AJUMS.REC.1398.580). This trial complies with the Declaration of Helsinki and was registered in the Iranian Registry of Clinical Trials (Registration ID: IRCT20090701002112N3).

Randomization and Blinding

Randomization was performed by blocked randomization with a block size of 6 and an allocation ratio of 1:1. Randomization sequences were computer-based by a coordinator (third party). The allocation process was concealed using sealed opaque envelopes, that had been prepared in advance. All envelopes were sequentially numbered and locked in the coordinating center, and the investigator opened each envelope, only at the time of the patient's allocation. Desmopressin and placebo were made identical in shape by a fourth party. The third party and fourth party were not involved in the clinical parts of the trial. Participants, investigators, and outcome assessors were unaware of the group assignment.

Participants

All patients with kidney disease, who were candidates for percutaneous native kidney biopsy and met the eligibility criteria, were informed about the trial and included, if they signed the written informed consent. Inclusion criteria were age between18 to 80 years old and 15 < eGFR < 90 mL/min/ 1.73m^2, estimated by Modification of Diet in Renal Disease [MDRD] Study equation. Exclusion criteria were impaired coagulation profile (platelet count < 50000 /µL, prolonged prothrombin time/international normalizing ratio (PT/INR)), blood pressure > 160/100 mmHg, single kidney renal cancer, hydronephrosis, Pyelonephritis, significantly small hyperechogenic kidneys on ultrasound study (i.e. < 9 cm adjusted length on ultrasound indicative of chronic irreversible disease), BMI > 30 kg/m^2, hemoglobin < 7 g/dL, plasma sodium < 135 meq/L, primary polydipsia, multicystic kidney disease, and transplant kidney. The following data were recorded: age, sex, blood pressure, blood group, Rh, hemoglobin, hematocrit, PT/INR, platelet count, serum creatinine, 24-hour urine collection findings, body mass index (BMI) (kg/m^2), and biopsy indication. Antiplatelet agents and heparin were held 7 days and 2 days before the biopsy, respectively.

Interventions

All eligible candidates were randomly assigned to either experimental (desmopressin acetate) or control (placebo) group. The experimental group were treated with 3 µg/kg of intranasal desmopressin acetate, and the control group were given with 1 ml/kg of intranasal sodium chloride solution 0.65%, one hour before the biopsy. Two interventional radiologists (one in each center) performed all biopsies, using a real-time ultrasound guidance, while patients were lying in the prone position. Two core kidney tissue samples were obtained from each patient, using an 18-gauge needle.

Objective

The primary objective was to evaluate the effect of pre-procedural desmopressin acetate administration on bleeding complications following ultrasound guided native kidney biopsy. Secondary objectives were the consequences of bleeding complications and the safety of desmopressin acetate.

Outcomes and Follow-up

The primary outcome was the bleeding complication events. Minor complications included perirenal hematoma and gross hematuria, and the major complications included arteriovenous fistula (AVF), acute renal obstruction, need for blood transfusion, endovascular embolization, sepsis, and death. Secondary outcomes were the hematoma volume (calculated by ultrasound as the products of length, width, and depth of the hematoma, expressed as mm^3), and changes in hemoglobin, hematocrit, plasma sodium and blood pressure. Post biopsy eGFR was checked, in case if a major complication occurred. Patients were completely immobilized for 24 hours after biopsy and the follow-up included clinical assessment (i.e., check for flank pain, gross hematuria, blood pressure, and heart rate), blood biochemistry evaluation (blood count, plasma sodium, and kidney function), and ultrasonographic assessment. In case of a perirenal hematoma formation, the follow-up ultrasound was performed as indicated. All adverse effects were recorded.

Sample Size

The sample size was calculated by comparing the proportion of two independent groups. Considering the P1 = 0.137, P2 = 0.305[30] (α: 0.05 and β: 0.2 (power: 80%)), the sample size was calculated 73 individuals within each group (total 146 patients).

Statistical Analysis

Analysis was by the intention-to-treat. Descriptive statistics were used to present the variable data as mean ± standard deviation (SD) or number (percentage). T-test was used for comparison of the quantitative, and chi-square test was used for comparing the categorical variables. The dependent t-test was used for pre-post differences of the quantitative variables, within each group. All statistical tests were 2-sided, and a *P* value of < .05 was considered statistically significant. All analyses were performed with SPSS, version 23 software.

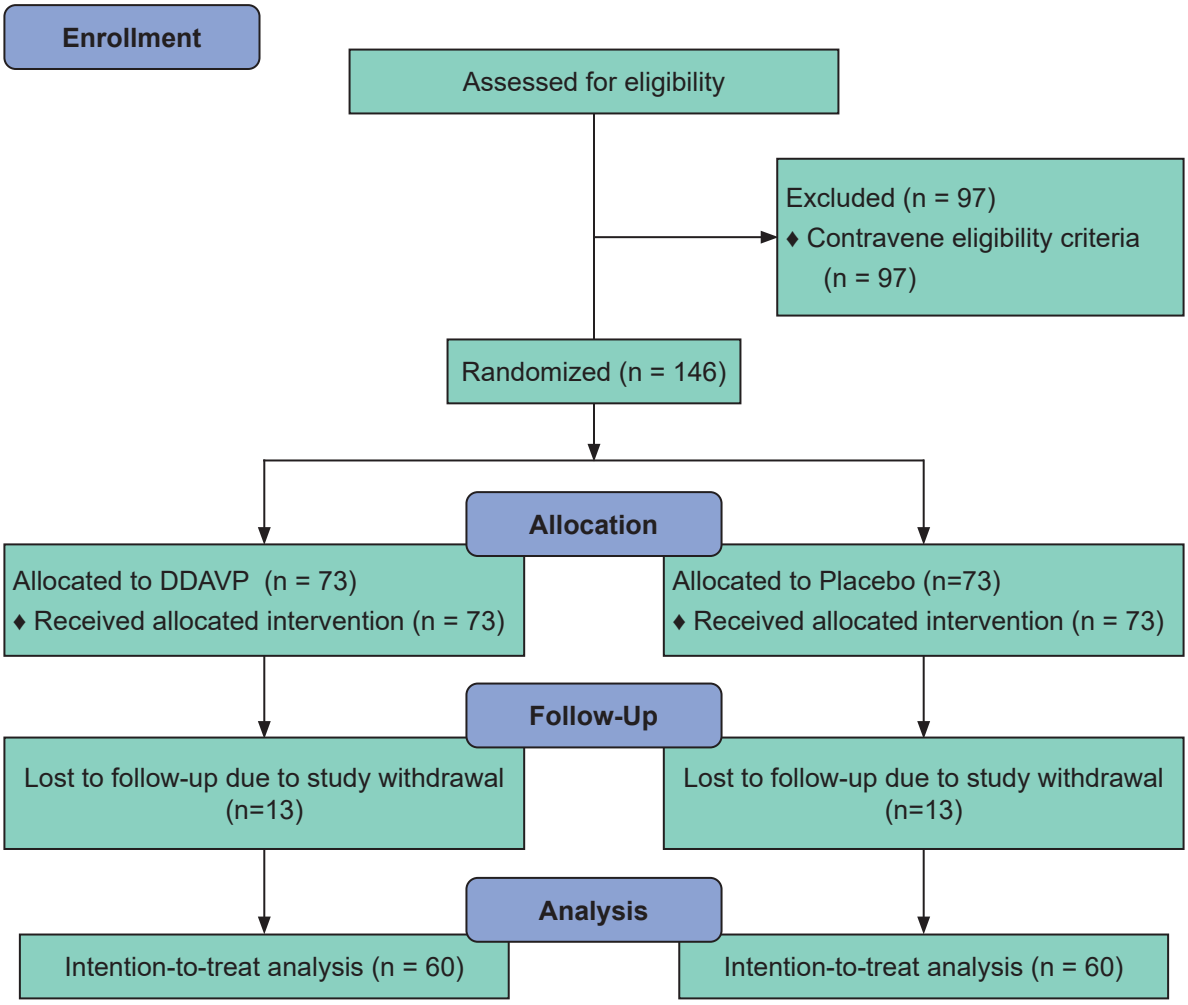
RESULTS

Baseline Characteristics

From July 2017 up to August 2020, 243 native renal biopsy candidates were assessed for eligibility criteria, out of which, 97 patients were excluded, because they met the exclusion criteria including impaired coagulation profile (n = 15), blood pressure > 160/100 mmHg (n = 29), small, hyperechogenic kidney on ultrasound (n = 3), single kidney (n = 5), renal cancer (n = 2), hydronephrosis (n = 8), pyelonephritis (n = 5), BMI > 30 kg/m^2 (n = 10), hemoglobin < 7 g/dL (n = 7), hyponatremia (n = 5), primary polydipsia (n = 2), and polycystic kidney disease (n = 6). Therefore, 146 patients, 73 cases within each group, were enrolled in the trial. During the study, 26 patients, 13 cases within each group, withdrew the study. Finally, the analysis was performed on a total of 120 patients, 60 patients within each group, including 58 men and 62 women with a mean age of 45.29 ± 15.95 years. Figure shows the Consolidated standards of reporting trials (CONSORT) diagram, depicting the flow chart of study participants. Baseline demographic and clinical characteristics of experimental (desmopressin) and control (placebo) groups are shown in table 1. As expected by the optimal randomization, there were no statistically significant differences, in demographic characteristics, between the two groups.

Study Outcomes

Table 2 shows the primary and secondary outcomes. The trial concluded that, pre-biopsy



Consolidated Standards of Reporting Trials (CONSORT) Diagram of the study

administration of DDAVP, significantly decreased post-biopsy hematoma incidence rates, as compared to placebo (7/60 [11.6%] vs. 24/60 [40%]; $P < .05$). Relative risk was 0.29 (95% CI: 0.183 to 0.423), the absolute risk reduction was 0.28 (95% CI: 0.175 to 0.412) and the number needed to treat was calculated about 4. The volume of perirenal hematoma was significantly smaller, in the desmopressin group who developed hematoma, compared to the placebo group (2.31 ± 1.17 vs. 7.72 ± 5.45 mm^3, $P < .05$). The frequency of gross hematuria rate was lower in the desmopressin group than the control group; however, the difference was not statistically significant (7/60 [11.6%] vs. 9/60 [15%], $P > .05$). Two patients in the desmopressin group and three patients in the placebo group developed AVF (2/60 [3.3%] vs. 3/60 [5%], $P > .05$). There was no statistically significant difference between the two groups, in terms of post-biopsy hemoglobin, hematocrit, serum sodium, and blood pressure changes.

Adverse Effect

All desmopressin-related adverse effects were recorded. Three patients reported transient mild headaches, two patients developed self-resolving cutaneous flushing, and one case developed transient self-resolving tachycardia. No case of hyponatremia, thrombotic event or volume overload occurred.

DISCUSSION

Kidney biopsy is the gold standard method for the diagnosis of kidney diseases. Although the ultrasound-guided percutaneous kidney biopsy is considered a low-risk procedure, post-biopsy

Table 1. Baseline Clinical and Demographic Characteristics

	Desmopressin Group (n (%))	Placebo Group (n (%))	*P*
Age, y	43.73 ± 16.88	46.85 ± 14.94	> .05
Sex			
Men	31 (51.7)	27 (45)	> .05
Women	29 (48.3)	33 (55)	
BMI, kg/m^2	25.98 ± 2.73	25.45 ± 3.38	> .05
Systolic Blood Pressure, mmHg	125.83 ± 11.5	125.74 ± 12.14	> .05
Diastolic Blood Pressure, mmHg	78.33 ± 6.15	79.5 ± 7.46	> .05
Heart Rate, /min	79.93 ± 6.66	80.75 ± 6.44	> .05
Hemoglobin, g/dL	11.39 ± 2.02	11.02 ± 1.9	> .05
Hematocrit	34.46 ± 5.57	33.11 ± 5.05	> .05
Platelet, cell number × 10^3/μL)	289 ± 89	275 ± 70	> .05
Prothrombin Time, second	12.46 ± 0.54	12.44 ± 0.68	> .05
International Normalized Ratio, Patient PT / Control PT^{ISI}	1.01 ± 0.05	1.04 ± 0.07	> .05
Serum Sodium, meq/L	140.83 ± 2.68	140 ± 3.59	> .05
Serum Creatinine, mg/dL	1.57 ± 0.81	1.92 ± 1.2	> .05
eGFR, cc/min/ 1.73m^2	54.14 ± 20.52	49.41 ± 15.63	> .05
Kidney Disease Patients			
AKI	3 (5)	6 (10)	> .05
CKD	21 (35)	22 (36.7)	
AKI on CKD	36 (60)	32 (53.3)	
Indications of Kidney Biopsy			
Isolated Proteinuria > 1 g/d	22 (36.7)	27 (45)	> .05
Microhematuria in Association with Proteinuria < 1g/day	0	3 (5)	
Microhematuria in Association with Proteinuria >1g/day	3 (5)	3 (5)	
Unexplained Kidney Dysfunction	32 (53.3)	21 (35)	
Kidney Abnormalities in Systemic Diseases	3 (5)	6 (10)	

Note. Data are presented as mean ± standard deviation or number (percentage).
Abbreviations: BMI, Body Mass Index; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; CKD, chronic kidney disease.

Table 2. Primary and Secondary Outcomes

Outcome Variable	Desmopressin Group	Placebo Group	*P*
Total Bleeding Events	14 (23.3%)	33 (55%)	< .05
Gross Hematuria	7 (11.7%)	9 (15%)	> .05
Perirenal Hematoma	7 (11.7%)	24 (40%)	< .05
Volume of Perirenal Hematoma, mm^3	1.17 ± 2.31	5.45 ± 7.72	< .05
Major Complications			
AVF	2 (3.3%)	3 (5%)	> .05
Others†	0	0	NA
Post Biopsy Hemoglobin, g/dL	11.21 ± 1.61	11.12 ± 1.73	> .05
Post Biopsy Hematocrit	34.36 ± 5.01	32.81 ± 5.13	> .05
Post Biopsy Serum Sodium, meq/L	140.35 ± 2.13	140.25 ± 3.12	> .05
Post Biopsy Systolic Blood Pressure, mmHg	126.39 ± 12.43	126.71 ± 11.98	> .05
Post Biopsy Diastolic Blood Pressure, mmHg	78.67 ± 6.28	79.92 ± 7.31	> .05

Note. Data are presented as mean ± standard deviation or number (percentage).
Abbreviations: AVF, arteriovenous fistula; NA, not applicable.
†Others: acute renal obstruction, blood transfusion; angiography, sepsis, and death.

bleeding may occur in as high as 34% of patients, which leads to prolonged hospital stay and increased treatment cost.[5,7,9] The bleeding risk is increased by advanced age, female sex, anemia, presence of bleeding diathesis, uncontrolled hypertension, and increased serum creatinine.[7,9,32] Therefore, the higher serum creatinine, the greater odds of bleeding complications.

To the best of our knowledge, this is the first randomized controlled trial that evaluated the

effect of desmopressin in bleeding complications, following ultrasound-guided percutaneous native kidney biopsy, in patients with the mean eGFR of 51.77 mL/min/1.73 m^2. The study showed favorable outcomes to support the effect of desmopressin administration in preventing bleeding complications.

Efficacy

This study showed that desmopressin administration in patients with reduced kidney function, significantly decreased bleeding complication events. In detail, the incidence of perirenal hematoma was significantly lower in desmopressin group and the rate of gross hematuria tended to be lower in the desmopressin group, though it was not significant. Furthermore, in case of perirenal hematoma formation, the volume was significantly smaller in the desmopressin group than in the placebo group. These results are consistent with the previous literature. Manno *et al.* performed a randomized controlled trial, and showed desmopressin administration in individuals with preserved kidney function, with the mean eGFR of 94.2 mL/min/1.73 m^2, decreased bleeding complications after percutaneous native kidney biopsy. Additionally, of the individuals who developed hematoma, the size of hematoma was significantly smaller in the desmopressin group.[30] Peters *et al.* conducted a prospective cohort on 576 native kidney biopsy candidates with a mean eGFR of 22.3 mL/min/1.73 m^2 and showed that, individuals who received pre-procedural desmopressin, experienced significantly fewer complications. Furthermore, multiple logistic regression analysis revealed that, prophylaxis with desmopressin causes less major (OR = 0.38, 95% CI: 0.15 to 0.96) and overall complications (OR = 0.36, 95% CI: 0.15 to 0.85).[33] Rao *et al.* investigated the efficacy of desmopressin in kidney biopsy candidates, with a mean eGFR of 35.6 mL/min/1.73 m^2. They showed that, the bleeding complications were significantly lower in the patients who received pre-procedure desmopressin. Additionally, the multivariate logistic regression model revealed that, not using desmopressin, was a significant predictor of post-biopsy bleeding events.[34] In studies by Leclerc *et al.* and Lim *et al.*, patients who received desmopressin had worse kidney function (eGFR of 28 vs. 45, in the Leclerc *et al.* study and 16.9 vs. 27.3, in the Lim *et al.* study). Despite the higher bleeding chance, desmopressin groups had a similar risk of complications, which further highlight the potential benefits of desmopressin.[35,36]

On the other hand, Athavale *et al.* reported that, desmopressin administration before kidney biopsy decreased the risk of bleeding in patients with a serum creatinine of ≥ 1.8 mg/dL and increased the risk, in those with serum creatinine of < 1.8 mg/dL. It seems that, the observed increased risk of bleeding, in patients with serum creatinine 1.8 mg/dL, was mainly concluded from the hemoglobin drop, influenced by dilutional change, rather than overt bleeding.[37] Cheong *et al.* reported a comparable risk of post kidney biopsy complications between patients who received desmopressin and those who did not.[38] Although their study was propensity-matched, it was limited by its retrospective observational nature and lack of a standardized protocol for desmopressin administration.

Safety

It was shown that, few mild and transient adverse effects were seen in the desmopressin group. As expected, based on well-defined eligibility criteria and study protocol, hyponatremia did not occur, which is concordant with existing literature.[30,33,34,36] Lower serum sodium levels before biopsy, periprocedural hydration protocol, and frequent diuretic use were the contributing factors to hyponatremia in some studies.[34,36]

Limitations

This study had several limitations. First, this trial enrolled patients with eGFR of 15 to 90 mL/min/ 1.73m^2, which may reflect a wide spectrum of eGFR; however, the mean eGFR was 51.7 mL/min/1.73m^2. Second, the trial met loss to follow-up, as 26 patients failed to complete the study; however, it was balanced between the study groups and it did not affect outcomes measurement. Third, few major complications occurred in this study, so we were unable to compare experimental and control groups in this regard. Considering the low incidence of major complications of about 1%,[7,8] a multi-center randomized trial, with large sample size is required to evaluate the efficacy of desmopressin administration, in reducing major complications.

CONCLUSIONS

This study concluded that desmopressin administration before percutaneous native kidney biopsy, is a safe and effective strategy to prevent bleeding complications. Considering absolute risk reduction of about 28%, the number needed to treat was about 4 procedures. We recommend considering desmopressin administration before percutaneous native kidney biopsy, in patients with a mean (SD) eGFR of 54.14 (20.52) mL/min/1.73m^2.

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None.

CONFLICT OF INTEREST

None.

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