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Original Investigation

Desmopressin Acetate in Percutaneous Ultrasound-Guided Kidney Biopsy: A Randomized Controlled Trial

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Background: Bleeding complications occur in one-third of percutaneous kidney biopsies and increase costs of the hospital stay. The aim of the study was to evaluate the effect of prebiopsy administration of desmopressin acetate versus placebo in the incidence of postbiopsy bleeding complications.

Study Design: Double-blind randomized controlled clinical trial.

Setting & Participants: We enrolled all patients with serum creatinine level ≤1.5 mg/dL and/or estimated glomerular filtration rate ≥60 mL/min/1.73 m^2 and normal coagulation parameters undergoing ultrasound-guided biopsy of the native kidney in our unit from August 2008 to December 2009.

Intervention: We examined prebiopsy subcutaneous administration of desmopressin acetate, 0.3 μg/kg, compared with placebo.

Outcomes & Measurements: The primary outcome was incidence of bleeding complications. Secondary outcomes were hematoma size, postbiopsy hemoglobin level, coagulation parameters, glomerular filtration rate, blood pressure, and length of hospital stay.

Results: 162 adult patients (88 men and 74 women) were enrolled; 80 were allocated to desmopressin treatment, and 82, to the placebo group. Desmopressin compared with placebo significantly decreased the risk of postbiopsy bleeding (11 of 80 [13.7%] vs 25 of 82 [30.5%]; relative risk, 0.45; 95% CI, 0.24-0.85; $P = 0.01$), hematoma size (median, 208 [25th-75th percentile, 120-300] vs 380 [25th-75th percentile, 270-570] mm^2; $P = 0.006$] in the 36 patients who experienced bleeding, and mean hospital stay (4.9 ± 1.1 vs 5.9 ± 1.7 days; $P = 0.004$); postbiopsy hemoglobin levels were not affected significantly in either group.

Limitation: Single-center design of the study.

Conclusions: Prebiopsy desmopressin administration decreases the risk of bleeding and hematoma size in patients undergoing percutaneous kidney biopsy without a cost increase.

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INDEX WORDS: Desmopressin; kidney biopsy; glomerular disease.

Editorial, p. 808

Percutaneous kidney biopsy in the diagnosis of primary and secondary kidney diseases is not a risk-free procedure, but technical advances in the methods of ultrasound guidance and automated-gun devices have decreased the associated risks.[1-6] However, accurate clinical, chemistry, and renal ultrasound evaluation before and 24 hours after kidney biopsy is necessary to check for bleeding complications. Our prior prospective study[7] is one of the few in this field that performed a systematic assessment of complications; these were still found to occur in about one-third of procedures, with major complications occurring in 1.2% of patients. The available literature has not established that a specific test can select patients with a major risk of postbiopsy bleeding.[8-11] Moreover, published studies do not show a potential and modifiable predictor of postbiopsy bleeding complications, and the impact of bleeding time on the complication rate is controversial.[7,12,13]

A synthetic derivative of the antidiuretic hormone vasopressin, desmopressin acetate (also referred to as 1-deamino-8-D-arginine vasopressin [DDAVP]), has been shown to be useful in a variety of inherited and acquired hemorrhagic conditions, including some congenital platelet function defects, chronic liver disease, uremia, and hemostatic defects induced by the therapeutic use of antithrombotic drugs, such as aspirin and ticlopidine.[14,15] The hemostatic effect of desmopressin is related to an increase in von Willebrand factor and factor VIII levels. Desmopressin is the treatment of choice for patients with von Willebrand (type I) disease and hemophilia A. In addition, desmopressin

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has been used as a hemostatic agent in patients undergoing surgery at major risk of bleeding.[15]

The aim of this study was to evaluate the effect of prebiopsy desmopressin acetate administration on the incidence of postbiopsy bleeding complications in patients undergoing ultrasound-guided percutaneous native kidney biopsy and with normal coagulation parameters.

METHODS

Study Overview

This is a phase 4, single-center, double-blind, randomized, controlled study in patients with kidney disease receiving ultrasound-guided percutaneous biopsy of the native kidney. The Independent Ethics Committee "Azienda Ospedaliero-Universitaria Consorziale Policlinico–Bari" approved the study protocol as an independent phase 4 research study in August 6, 2008. The study was carried out according to the Declaration of Helsinki (IV Adaptation). Patients who gave written informed consent were included in the study.

Participants and Setting

All consecutive in-patients of both sexes who satisfied the eligibility criteria were asked to participate in the study. Inclusion criteria were patients undergoing percutaneous ultrasound-guided biopsy of the native kidney in our unit who were aged 16-80 years with blood pressure $<$140/90 mm Hg with or without antihypertensive therapy, serum creatinine level $\leq$1.5 mg/dL and/or estimated glomerular filtration rate (GFR) $\geq$60 mL/min/1.73 m^2 (calculated using the Modification of Diet in Renal Disease [MDRD] Study equation), and normal coagulation parameters (bleeding time evaluated using the Simplate method, with values for prothrombin time, partial thromboplastin time, platelets, and fibrinogen in the reference range). Exclusion criteria were solitary kidney, kidney cancer, hydro-/pyonephrosis, significantly decreased kidney size on ultrasound image, severe obesity (body mass index $>$30 kg/m^2), and acute kidney injury. Medications that could interfere with hemostasis were withdrawn before the procedure: antiplatelet agents at least 7 days before and heparins 1-2 days before the kidney biopsy.

Interventions

All eligible patients were randomly assigned to the experimental (desmopressin acetate) or control (placebo) group. The experimental group was treated using desmopressin acetate (subcutaneously, dosage of 0.3 μg/kg) 1 hour before the kidney biopsy. The control group was treated with placebo (subcutaneously, 1 mL of saline solution). Kidney biopsies were performed by an experienced nephrologist (C.M.), ultrasound evaluation and primary outcome were assessed by an expert in kidney ultrasonography (N.C.), randomization was performed by a third investigator (C.B.), therapy was administered by a nurse not involved in the study, and data collection and statistical analysis was performed by a fourth investigator (D.D.T.). All biopsies were performed using real-time ultrasound-fixed guidance (4.0-MHz convex probe, Acuson Sequoia 512; Siemens Medical Solutions, www.siemens.com) and a 16-gauge automated spring-loaded gun (Bard Monopty; Bard Peripheral Vascular Inc, www.bardpv.com). A pathologist promptly examined the specimens under light microscopy to obtain renal tissue sufficient for light, immunofluorescence, and electron microscopy studies.

Objectives

The primary objective was to evaluate the hemostatic efficacy of prebiopsy treatment with desmopressin. Secondary objectives were to determine the effects of bleeding complications, potential predictors of bleeding complications, and the safety of desmopressin administration.

Outcomes and Measurements

The primary outcome measure was the incidence of postbiopsy bleeding complications. Minor complications included perirenal hematoma of at least 20 $\times$ 20 mm and gross hematuria that resolved spontaneously without interventions. Major complications were arteriovenous fistula formation; acute renal obstruction; rapid decrease in hemoglobin level requiring blood transfusion, angiography, and gel-foam transarterial embolization; sepsis; or death. Secondary outcome measures were hematoma size (computed as the products of the longest and shortest diameters on the bidimensional picture), postbiopsy hemoglobin level, coagulation parameters, GFR, blood pressure, and length of hospital stay. The following data were collected: age, sex, blood pressure, hemoglobin level, hematocrit, bleeding time, prothrombin time, partial thromboplastin time, fibrinogen level, platelet level, serum creatinine level, 24-hour proteinuria, serum and urinary electrolyte levels, serum and urinary osmolarity, and numbers of passes, cores, and total glomeruli. Postbiopsy follow-up was represented by clinical evaluation (blood pressure, heart rate, flank pain, and gross hematuria), chemistry (blood count and kidney function), and ultrasound evaluation immediately and 24 hours postbiopsy, per protocol.

Sample Size

Sample size was calculated by the difference in postbiopsy bleeding complications. No study was available in the literature about the efficacy of desmopressin for bleeding complications in patients undergoing kidney biopsy. Because the presence of bleeding was shown in $\sim$30%-40% of a prospective cohort in our previous observational study, we hypothesized as clinically relevant a decrease in risk of 0.50 and an absolute decrease in risk from 0.40 to 0.20.[7] The sample size of the study for power of 0.80 and significance level $<$0.05 was calculated in 158 patients (79 for each group). However, we increased the sample size to 162 patients to avoid unexpected losses to follow-up, such as withdrawal of consent, early discharge, or late objections to kidney biopsy or drug administration.

Randomization

A 1:1 allocation assignment sequence was generated using random-number tables; a list divided into blocks of 10 was adequately concealed to prevent attempts to subvert randomization. Block randomization was by a computer-generated random number list prepared by an investigator with no clinical involvement in the trial.

Blinding

Masking of the study included subjects, investigators, and outcome assessors, including the ultrasound reader. In addition, nurses who prepared and administered the drugs were blinded.

Follow-up and Monitoring

All patients were observed in the postbiopsy follow-up: screening ultrasound was performed in all patients who underwent kidney biopsy, the procedure was performed immediately and 24 hours postbiopsy in all patients, and it was the standard for everyone. In the case of hematoma formation, patients were evaluated again after 48 and 72 hours, if necessary. All adverse events and side effects of the drug were recorded. Patients were

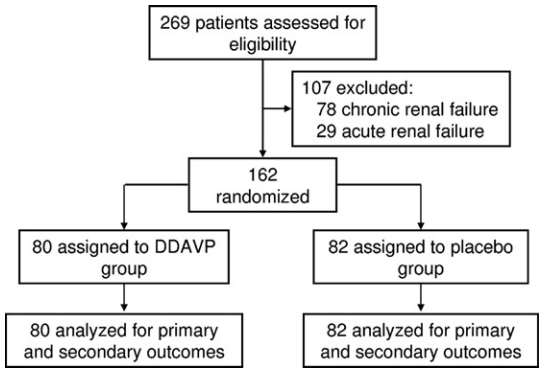

Figure 1. Flow diagram. Abbreviation: DDAVP, desmopressin acetate (1-deamino-8-D-arginine vasopressin).

maintained on strict bed rest for at least 24 hours after the procedure.

Statistical Analysis

Results are expressed as mean ± standard deviation or median and interquartile range (25th, 75th percentile) for continuous data and as integers, frequencies, and percentages for categorical data. Continuous data were evaluated using unpaired and paired Student *t* test, Mann-Whitney *U* test and Wilcoxon test, whereas for categorical data, χ^2 or Fisher exact test were used. Relative risks and their 95% confidence intervals (CIs) were reported. Analysis was conducted by intention to treat. All analyses were performed using SPSS for Windows, release 17.0 (SPSS Inc, www.spss.com); $P < 0.05$ is considered statistically significant.

RESULTS

Baseline Characteristics

From August 2008 to December 2009, a total of 162 patients (88 men and 74 women) with a mean age of 40.6 ± 14.6 years undergoing native kidney biopsy in our renal unit were enrolled; 80 were allocated to desmopressin acetate treatment, and 82, to the placebo group. The flow diagram is shown in Fig 1. Two hundred sixty-nine patients were assessed for eligibility; 107 of them were excluded because they did not fulfill the inclusion criteria. All patients were analyzed for the primary and secondary outcomes. Baseline demographic and clinical characteristics of the experimental and control groups are listed in Table 1; there were no statistically significant differences between

Table 1. Baseline Demographic and Clinical Characteristics

	Desmopressin Group	Placebo Group	*P*
No. of patients	80	82	
Age (y)	39.5 ± 14.2	41.7 ± 15.0	0.3
Men/women	45:35	43:39	0.6
Body weight (kg)	69.6 ± 13.0	68.9 ± 14.1	0.7
Systolic blood pressure (mm Hg)	126.8 ± 13.6	128.3 ± 12.5	0.5
Diastolic blood pressure (mm Hg)	80.9 ± 9.3	82.6 ± 9.3	0.2
Hemoglobin (g/dL)	13.9 ± 1.8	13.5 ± 1.8	0.1
Platelets ($\times 10^3/\mu$L)	262 (224, 299)	256 (208, 288)	0.5
Prothrombin time (ratio)	1.0 ± 0.1	1.0 ± 0.1	0.9
Partial thromboplastin time (ratio)	1.0 ± 0.1	1.0 ± 0.1	0.3
Fibrinogen (mg/dL)	337 (267, 430)	326 (271, 406)	0.4
Bleeding time (min)	4.6 ± 1.2	4.5 ± 1.2	0.7
Serum creatinine (mg/dL)	1.0 ± 0.3	1.0 ± 0.2	0.3
Proteinuria (g/24 h)	1.1 (0.4, 3.3)	1.1 (0.4, 2.9)	0.2
eGFR (mL/min)	94.2 ± 22.8	89.4 ± 21.3	0.2
Clinical indication for kidney biopsy			0.5
Recurrent machrohematuria and/or urinary abnormalities (proteinuria, microhematuria)	53	58	
Nephrotic syndrome	27	24	
Histologic diagnosis (no.)			0.7
Glomerulonephritis	61	64	
Benign nephrosclerosis	8	9	
Interstitial nephritis	0	1	
Amyloidosis	5	3	
Diabetic nephropathy	3	0	
Others	3	5	

Note: Data are expressed as mean ± standard deviation, median (25th, 75th percentile), or absolute frequency. Conversion factors for units: hemoglobin in g/dL to g/L, ×10; fibrinogen in mg/dL to μmol/L, ×0.0294; serum creatinine in mg/dL to μmol/L, ×88.4; eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667; no conversion needed for platelets in $10^3/\mu$L and 10^9/L.

Abbreviation: eGFR, estimated glomerular filtration rate.

the 2 groups, as expected by a proper randomization. Clinical indications for performing kidney biopsy were recurrent macrohematuria and/or urinary abnormalities (proteinuria and microhematuria) in 111 patients (69.5%) and nephrotic syndrome in 51 patients (31.5%). There were no significant differences between the experimental and control groups in number of passes (median, 2 [25th-75th percentile, 2.0-3.0] for both groups; $P = 0.6$), cores (median, 2 [25th-75th percentile, 2.0-2.0] for both groups; $P = 0.5$), and total glomeruli obtained (median, 21.0 [25th-75th percentile, 15.0-26.0] and 19.5 [25th-75th percentile, 15.0-25.0], respectively; $P = 0.4$). There was no case of inadequate sampling (<7 glomeruli) at kidney biopsy.

Primary and Secondary Outcomes

Outcomes data are listed in Table 2. Administration of desmopressin compared with placebo significantly decreased the risk of postbiopsy bleeding (11 of 80 [13.7%] vs 25 of 82 [30.5%]; $P = 0.01$). Relative risk was 0.45 (95% CI, 0.24-0.85). The absolute reduction in risk was 0.17 (95% CI, 0.09-0.32), whereas the number needed to treat was 5.98 (95% CI, 3.16-11.30). In 36 patients who experienced a bleeding complication, the hematoma was significantly smaller in the desmopressin group than in the placebo group (median, 208 [25th-75th percentile, 120-300] mm^2 vs 380 [25th-75th percentile, 270-570] mm^2; $P = 0.006$). There were no differences in values for hemoglobin, coagulation parameters, estimated GFR, or blood pressure after the biopsy procedure between the experimental and control groups. Furthermore, no change in postbiopsy hemoglobin levels was seen in either group. No patient showed gross hematuria or arteriovenous fistula formation. No patient required transfusion, angiography, and/or embolization or nephrectomy. Two patients in the control group experienced moderate lumbar pain. However, mean hospital stay was longer in the control group than the desmopressin group (5.9 ± 1.7 vs 4.9 ± 1.1 days; $P = 0.004$).

Adverse Events

Adverse events and side effects of the drug were recorded on the report form. No serious adverse events occurred. Three patients experienced a transient (<1 hour) mild increase (<5%) in heart rate. No patient showed hyponatremia, alterations in blood pressure, or episodes of thromboembolism.

DISCUSSION

In this single-center double-blind randomized controlled trial in patients with kidney disease undergoing ultrasound-guided percutaneous kidney biopsy, we evaluated the effect of prebiopsy treatment with desmopressin acetate on the incidence of postbiopsy bleeding complications. Results show that desmopressin administration in patients with preserved kidney function and absence of coagulation disorders significantly decreased the risk of bleeding complications after kidney biopsy procedures, mainly hematoma formation. Furthermore, in patients who experienced bleeding, hematomas were smaller in the desmopressin group than the placebo group, although hemoglobin levels pre- and postbiopsy did not change significantly in either group. On the contrary, in a recent report, hematoma size immediately after biopsy was associated with decreased hemoglobin level.[16]

Table 2. Primary and Secondary Outcomes

Outcome	Desmopressin Group	Placebo Group	*P*
No. of patients	80	82	
Hematoma	11/80	25/82	0.01
Gross hematuria	0/80	0/82	NA
Major complications[a]	0/80	0/82	NA
Lumbar pain	0/80	2/82	0.4
Postbiopsy hemoglobin (g/dL)	13.4 ± 1.6	13.1 ± 1.8	0.3
Hemoglobin change (g/dL)	0.5 ± 0.6	0.4 ± 0.6	0.2
Size of hematoma (mm^2)	208 (120, 300)	380 (270, 570)	0.006
Postbiopsy eGFR (mL/min)	93.8 ± 22.1	89.2 ± 21.7	0.2
Postbiopsy systolic blood pressure (mm Hg)	126.9 ± 12.0	126.2 ± 12.6	0.7
Postbiopsy diastolic blood pressure (mm Hg)	80.6 ± 7.6	81.3 ± 7.9	0.5
Length of hospital stay (d)	4.9 ± 1.1	5.9 ± 1.7	0.004

Note: Data expressed as mean ± standard deviation, median (25th, 75th percentile), or absolute frequency. Conversion factors for units: hemoglobin in g/dL to g/L, ×10; eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667; no conversion needed for platelets in $10^3/\mu L$ and $10^9/L$.

Abbreviations: eGFR, estimated glomerular filtration rate; NA, not applicable.

[a]Arteriovenous fistula, transfusion, angiography and/or embolization, and nephrectomy.

Administration of desmopressin has been reported to shorten bleeding time and prevent bleeding complications in patients with uremia.[17] Moreover, desmopressin has been useful in patients with a variety of inherited and acquired hemorrhagic conditions and high-risk obese patients undergoing percutaneous kidney biopsy.[14,15,18] A randomized controlled trial could be unethical in high-risk patients; thus, desmopressin use is accepted nearly universally in this setting. However, administration of desmopressin may be accompanied by water retention and hyponatremia, decrease in blood pressure, and secondary increase in heart rate.[19] In patients undergoing cardiac surgery, desmopressin was not as effective as other methods in preventing blood loss and was associated with increased thrombotic risk.[15] Thrombotic events also were reported as rare side effects of the drug in another study.[20] For all these important reasons, desmopressin use in patients without kidney failure and coagulation disorders should be demonstrated by a randomized controlled trial with adequate statistical power.

Several studies, often retrospective and uncontrolled, have shown that real-time ultrasound-guided kidney biopsy and automated-gun devices have improved the safety of the kidney biopsy procedure.[21-26] Such reports have focused on the relative merits of different kidney biopsy techniques and types of needles, but to our knowledge, no study has shown potential predictors of postbiopsy bleeding complications. However, despite these technical advances, in a recent observational prospective study, we showed that bleeding complications arise in one-third of the procedures, although major complications were observed in only 1.2% of patients.[7] Of the data available to us, only sex, age, and baseline partial thromboplastin time showed a significant predictive value.[7] Because sex and age are nonmodifiable factors and the increase in partial thromboplastin time remained in the reference range, we planned a randomized controlled trial. The aim was to eliminate the incidence of major complications and significantly decrease minor complications. These latter, although not clinically relevant, increase the patient's anxiety and may increase the costs of hospitalization in terms of mean hospital stay and ultrasonographic and laboratory tests. In our study, patients treated with desmopressin remained in the hospital on average 1 day less than patients treated with placebo, with an average cost saving of ~€555 ($758.5). However, the cost of the drug in each procedure was only €68.5 ($93.6). In this approximate cost-benefit analysis, administration of the experimental drug was not associated with increased cost of hospitalization, but the present analysis is insufficient to draw definitive conclusions. To our knowledge, this is the first randomized controlled trial that shows the efficacy of desmopressin in percutaneous kidney biopsy to decrease bleeding complications in patients without coagulation disorders. Because the absolute reduction in risk in our trial is ~20%, the number needed to treat is ~6 procedures. We believe that these results are clinically relevant to optimize procedures related to kidney biopsy. However, it is obvious to recommend mandatory use of desmopressin in patients with bleeding disorders. In high-risk patients, the use of other procedures, such as transjugular renal biopsy or laparoscopic kidney biopsy, also may decrease hemorrhagic complications.[27-29]

A possible limitation of the study is the single-center design, which could decrease the generalizability of our results and their external validity. However, the absence of adverse events and mild side effects observed in our study may recommend the administration of desmopressin in all patients who undergo kidney biopsy. Collection of additional data may confirm the findings of our study and thus adoption of our recommendations in international guidelines.

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