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Randomized Double-Blind Placebo-Controlled Trial of Desmopressin for Post–Kidney Biopsy Bleeding

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Introduction: This study evaluated the efficacy and safety of desmopressin in reducing postbiopsy bleeding in patients undergoing kidney biopsy, a common complication requiring effective prevention strategies.

Methods: In this double-blind, randomized, placebo-controlled trial conducted from February 2019 to January 2023 at a teaching institute in Lucknow, India, 203 patients aged 18 to 65 years undergoing indication kidney biopsy were randomized to receive desmopressin (300 μg) or placebo intranasally an hour before the procedure. Outcomes included postbiopsy bleeding (primary) and hemoglobin drop, hypotension, hematuria, hematoma, transfusion need, and radiological or surgical interventions (secondary).

Results: Bleeding incidence was significantly lower in the desmopressin group (11.9%) compared with placebo (33.3%, $P = 0.0003$). Hematoma formation was reduced (11.9% vs. 30.4%, $P = 0.001$), with a relative risk (RR) of bleeding of 0.356 (95% confidence interval [CI]: 0.196–0.648, $P = 0.0007$). Stratified analysis showed reduced bleeding across estimated glomerular filtration rate (eGFR) categories (> 30 and < 30 ml/min per 1.73 m^2), with numbers needed-to-treat of 5.667 and 3.978, respectively. Hyponatremia and headaches were more frequent in the desmopressin group. Factor VIII and von Willebrand factor (vWF) levels were significantly elevated 2 and 4 hours after administration. No serious adverse events occurred.

Conclusion: Desmopressin effectively reduces postbiopsy bleeding and hematoma formation with manageable side effects, supporting its role as a prophylactic option in kidney biopsies. Further studies are needed to confirm its broader clinical applications.

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Percutaneous ultrasound-guided kidney biopsies are the gold standard for diagnosing kidney parenchymal disease in native and transplant kidneys. Kidney biopsies assist in histological diagnosis, optimal treatment, and prognosis. It became safer with the inclusion of ultrasound guidance and automated biopsy gun devices; still, postbiopsy bleeding remains a major concern for nephrologists and interventional radiologists doing kidney biopsies.[1] Other than age, gender, hypertension, and coagulopathy, uremia is a significant risk factor for post–kidney biopsy bleeding.[2] Uremia is associated with prolonged bleeding time, which may be the result of an abnormality in platelet function, endothelial dysfunction, or defective platelet-vessel wall interaction, mainly because of decreased vWF.[3] Factor VIII circulates with vWF, and often, the levels of these 2 clotting factors are similarly affected by stress, inflammatory states, or endothelial dysfunction, a common manifestation of uremia.

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Desmopressin acetate or 1-deamino-8-D-arginine-vasopressin, a synthetic analog of vasopressin with minimal vasoconstrictor properties, has been found effective in treating bleeding disorders such as von Willebrand disease and hemophilia.[4] Desmopressin induces the release of vWF from endothelial storage and factor VIII and thus improves platelet-vessel wall interaction. It acts as a selective agonist of endothelial vasopressin-2 receptors, augmenting factor VIII and vWF plasma levels. These biological effects of desmopressin acetate and cryoprecipitate on these hemostatic proteins led some investigators to postulate that desmopressin might be therapeutically effective in reducing uremic bleeding.

Studies have demonstrated that administration of desmopressin elicits a rapid but transient increase in the circulating levels of vWF and factor VIII, reaching a peak between 90 minutes and 120 minutes after administration. A single dose of desmopressin is expected to increase the factor VIII level by 3- to 6-folds.[5] The other effects of desmopressin include vasodilation and an oxytocic effect at lower intranasal doses of 15 to 20 μg. It can also be administered by i.v. (0.3–0.4 μg/kg), and subcutaneous (0.3 μg/kg) routes. It improves bleeding time within 1 hour, and the effect is maintained for 4 to 8 hours.[4] It has been shown to normalize bleeding time in uremia for up to 4 to 8 hours, presumably through its vasopressin-2 receptor agonist activity. Side effects include flushing, headache, water intoxication, dilutional hyponatremia, and thrombotic events.[6] The major limitation is tachyphylaxis after 2 to 3 doses.[7] However, it is used in a single dose before biopsy.

The existing data shows the conflicting impact of desmopressin's effectiveness in reducing uremic bleeding. Some studies have shown a benefit in using desmopressin, particularly in high-risk patients, though the definition of "high risk" varies across studies.[8-11] Surprisingly, 1 study indicated harm when used in low-risk patients but demonstrated a benefit for high-risk patients.[12] Moreover, there are only 3 underpowered randomized controlled studies,[9,13] whereas the rest are mainly observational.[8] In another interesting observational study, Leclerc *et al.*[11] reported that those who received desmopressin had similar rates of postbiopsy bleeding but lesser need on radiological interventions, even though they had lesser mean eGFR than patients who did not receive desmopressin. No study has demonstrated an effect on factor VIII and vWF after desmopressin in the biopsy period.

We conducted a double-blind, randomized controlled trial (RCT) to establish the role of desmopressin acetate in reducing the risk of postbiopsy bleeding in patients undergoing kidney biopsy, either with normal or low eGFR.

METHODOLOGY

We conducted a double-blind, randomized, placebo-controlled clinical trial between February 1, 2019 and January 1, 2023 at the Nephrology Department of the Sanjay Gandhi Postgraduate Institute of Medical Sciences, a large volume referral teaching institute in Lucknow, Uttar Pradesh, India.

Study Participants

All adult patients aged between 18 and 65 years, undergoing kidney biopsy of the native kidneys for any indication were screened for inclusion in the study. All patients had an indication kidney biopsy for unexplained glomerular hematuria, proteinuria (nephrotic or subnephrotic range proteinuria), or unexplained renal failure to establish the diagnosis. Patients with any baseline eGFR were included in the study.

Those with coronary artery disease, congestive cardiac failure, gross ascites, hydroureteronephrosis, solitary kidney or congenital anomalies of the kidney and urinary tract, established chronic kidney disease and bilateral small kidneys (size $<$ 9 cm), kidney transplant recipients, pregnant women or postpartum state up to 42 days, patients with obesity unable to hold the breath or psychiatric disorders, hyponatremia ($Na+ <$ 130 mmol/) on the day before the procedure, patients on anticoagulants or antiplatelet agents, thrombocytopenia (platelet count $<$ 1 million/mm^3), coagulopathy defined as International normalized ratio $>$ 1.5 times elevation or activated partial thromboplastin time $>$ 40, or inability to give or unwilling to consent were excluded from the study. Patients requiring dialysis were eligible if their previous dialysis session had been completed at least 24 hours before the planned kidney biopsy and only if the dialysis session had been done free of heparin administration (Supplementary Table S1).

The Kidney Biopsy Procedure

All kidney biopsies were performed using a percutaneous technique with real-time ultrasound on Toshiba, Japan, and Xario model SSA-660a, with a 3.75 MHz curvilinear probe. All biopsies were performed using spring-loaded automated devices (Bard Peripheral Vascular Inc., USA – "BARD Max-core disposable core biopsy needle") with 18 gauge and 16 cm long needle with a penetration depth of 22 mm and sample notch of 18 mm. All biopsies were performed by nephrologists with real-time ultrasound imaging and needle tracking from the lower pole of either kidney with a needle guide (Ultra-pro II Needle guide, Civco, IA).

Two individuals were involved in carrying out all the biopsies. One consultant nephrologist who operated the ultrasound machine selected the best ultrasound window for approaching the kidney and guided the needle. The second was a trainee in nephrology who handled the above-mentioned automated device and performed the trigger under the supervision of the former. The biopsy yields, complication rates, number of needle-passes to obtain 2 cores of biopsy samples, and percentage of cortex and medulla of each on histopathology were all noted. The percentage of cortex and medulla was independently evaluated by 2 histopathologists, and the mean of the 2 values was considered final. The renal biopsy tissue specimen handling evaluation was done as per institute protocols.

Randomization, Blinding, and the Intervention

All those patients who fulfilled the criteria for the study were assigned into 2 different groups using a computer-generated random number table in a 1:1 ratio. Patient enrollment was stratified based on an eGFR cut-off of 30 ml/min per 1.73 m^2 to ensure an equal distribution of patients on either side of this threshold. Patients and biopsy-performing nephrologists were blinded to the intervention. Patients were assigned by randomization to the study drug desmopressin and placebo (normal saline) packed in a similar-looking package. Allocation concealment was done by sealed sequentially numbered opaque envelopes. These were consecutively numbered, and the medication was given out according to the number allocated to the participant by a clinical nurse coordinator trained for the purpose. A total of 300 μg, 150 μg in each nostril, was administered 1 hour before the procedure. The number of puffs was calculated as per the delivered dose mentioned on the packet insert of the drug. The placebo was locally manufactured and packed in an identical appearing container and nozzle.

The investigator was blinded to the allotment because the procedure was carried out by a third person, a clinical coordinator employed for this purpose. The study drug and placebo were given through the intranasal route 1 hour before the procedure.

Follow-up Evaluation and Monitoring

After the kidney biopsy, patients were kept on strict bed rest until they passed urine and observed in hospital for 24 hours and followed-up as per standard institute protocol. Vitals were recorded prebiopsy and immediately after the procedure, with an interval of 30 minutes up to 2 hours, then hourly for 6 hours, and then 3 hours up to the next 18 hours, as per institute protocol. Hemoglobin and hematocrit were monitored at 1 hour before prebiopsy, at 4 hours, and 24 hours postbiopsy. Serum creatinine and eGFR as per the Chronic Kidney Disease Epidemiology Collaboration equation, were calculated at baseline and as required by the treating clinician. A screening ultrasonogram for postbiopsy perinephric hematoma was done immediately after the biopsy and 24 hours afterwards by radiologist, not initially involved while doing the biopsy. In cases of postbiopsy bleeding, more frequent and prolonged monitoring was done as per the patient's needs. All drug-related adverse effects were recorded.

Quantification of vWF, Factor VIII, and Thromboelastographic Analysis

Venous blood was collected at the following 3-time points: 0 hours just before giving desmopressin, 2 hours, and 4 hours after desmopressin or placebo administration. Four ml of blood was collected in 2 sodium citrate (3.2%) vials (one for vWF and factor VIII and the other for thromboelastographic) at each time interval. Plasma was separated after collection to measure vWF and factor VIII concentrations and stored at -20 °C until further processing.

Outcome Measures

The primary outcome was the occurrence of postbiopsy bleeding. Postbiopsy bleeding was categorized as either major or minor. Major complications include bleeding requiring blood transfusion, nephrectomy, gel foam embolization, coiling, hypotension, and death. Minor complications included gross hematuria or subcapsular perinephric hematoma, which spontaneously resolved without the need for further intervention. The primary outcome was defined as the number of patients who experienced postbiopsy bleeding, irrespective of the number or type of bleeding manifestations. A single patient could have multiple bleeding associated events (e.g., hematoma, hematuria, etc.), and they were counted as 1 for the primary outcome analysis.

Secondary outcomes included the individual components of postbiopsy bleeding, namely hematoma, hematuria, decrease in hemoglobin > 1 g/dl, hypotension, need for transfusion, and radiological intervention, and these were analyzed individually.

Categorization Into eGFR Groups

The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[14] They were categorized into 5 groups, that is, eGFR > 90 ml/min per 1.73 m^2, eGFR of 60 to 89 ml/min per 1.73 m^2, eGFR of 45 to 59 ml/min per 1.73 m^2, eGFR of 30 to 44 ml/min per 1.73 m^2, eGFR 15 to 29 ml/min per 1.73 m^2, and eGFR < 15 ml/min per 1.73 m^2.

Enzyme-Linked Immunosorbent Assay for Factor VIII and vWF Estimation in Brief

The plasma was isolated by centrifugation of blood collected in the ethylenediaminetetraacetic acid vial at

1500 rpm for 10 minutes. The isolated plasma was stored at −20 °C until the enzyme-linked immunosorbent assay analysis was done.[15] The detailed procedure has been explained in the Supplementary File.

TEG Analysis

All patients were subjected to TEG before kidney Biopsy. Kaolin-activated TEG was done using TEG 5000 Thrombelastograph HemostasisAnalyzer System (Haemonetics Corporation USA) from the whole blood following the standard operating procedures given by the manufacturer.[14] TEG results were expressed in terms of reaction time, kinetic time, alpha angle, maximum amplitude, and lysis at 30 minutes after maximum amplitude (Supplementary Figure S1).

Sample Size Calculation and Statistical Analysis

To detect the difference in proportions between the 2 study groups, the proportion of patients who experienced bleeding in the desmopressin and placebo groups was 13.7% and 30.5%, respectively.[9] Considering the 80% statistical power of the study and minimum 2-sided 95% CI, the minimum required sample size in each of the 2 groups came out to be 95. Finally, we planned to include 200 patients: 100 patients in the desmopressin group and 100 in the placebo group. Furthermore, randomization was stratified based on an eGFR cut-off of 30 ml/min per 1.73 m^2 to ensure an equal distribution of patients on either side of this threshold. This approach was based on findings from previous studies, including one from our center, which found a significant increase in the adjusted RR for bleeding when the glomerular filtration rate falls below 30 ml/min per 1.73 m^2. [11,16] The numbers needed-to-treat to prevent 1 bleeding complication in patients in both categories were calculated. The sample size was estimated using the software G Power version, which was 3.1.9.2 (Düsseldorf University, Germany). Continuous data are presented in mean ± SD or median (interquartile range), while categorical data is in frequency (percentage). Kolmogorov Smirnov test was used to determine the distribution of data. A *t* test was used to compare the mean values between the groups. The chi-square test, or Fisher exact test, was used to compare the categorical values between the groups, as per the required application. IBM SPSS statistics for macOS, version 25.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data.

Clinical Trial Registry, Ethical Approval, and Funding Declaration

The study was registered with The Clinical Trials Registry- India (CTRI), https://ctri.nic.in, with approval number CTRI/2019/08/020894. The institute ethics committee approved the study, approval number 2019-114-IMP-109. The study was funded by an intramural grant from the institute, grant number A-10-PGI/IMP/80/2019.

RESULTS

A total of 1200 patients for indication kidney biopsies were screened for eligibility in the study. Two hundred three patients who were found eligible as per the inclusion and exclusion criteria were randomized to receive either desmopressin (n = 101) or placebo (n = 102) (Figure 1). The mean age was 40.6 (± 15.21) years, and 62.5% were males. The mean body mass index was 24.66 (± 6.51), and the median (interquartile range) eGFR at which the biopsy was done was 30 (16–71) ml/min per 1.73 m^2. The baseline clinical and laboratory characteristics were comparable between desmopressin and placebo groups and are presented in Table 1.

Major and Minor Complications Post–Kidney Biopsy

The overall incidence of bleeding was significantly lower in patients in the desmopressin group (12 [11.9 %]) compared with placebo (34 [33.3%], P = 0.0003) (Table 2, Supplementary Table S2). Overall, the RR of bleeding in the desmopressin group was 0.356 (95% CI: 0.196–0.648), P = 0.0007) lower than that of the placebo group. Hematomas were significantly more common in the placebo group (30.4%) than in the desmopressin group (11.9%) (P = 0.001), with the mean hematoma size being larger in the placebo group (3.51 cm) compared with the desmopressin group (2.12 cm, P = 0.01) (Table 2). The requirement for interventional radiological procedures to control the bleeding was 1 in each group, and both patients had eGFR < 15 ml/min per 1.73 m^2 (Table 2). The need for packed red blood cell transfusion did not differ significantly between the 2 groups (2.94% placebo vs. 4.95% desmopressin, P = 0.46) (Table 2). There was a significant difference in the decrease of hemoglobin greater than 1 g/dl, with the desmopressin group showing a higher incidence (30.69 %) than the placebo group (17.64%) (P = 0.03). Hemoglobin values at different time points have been highlighted in (Supplementary Figure S2).

Postbiopsy Bleeding Stratified According to eGFR

On stratifying the bleeding incidence as per eGFR categories, we found that for patients with eGFR > 30 ml/min per 1.73 m^2, bleeding was significantly lower in the desmopressin group (5.9%) compared with placebo (23.5%) (P = 0.01). The RR of bleeding in the desmopressin group was lower (RR: 0.25 [95% CI: 0.075–0.833]), P = 0.02) than in the placebo patients. The

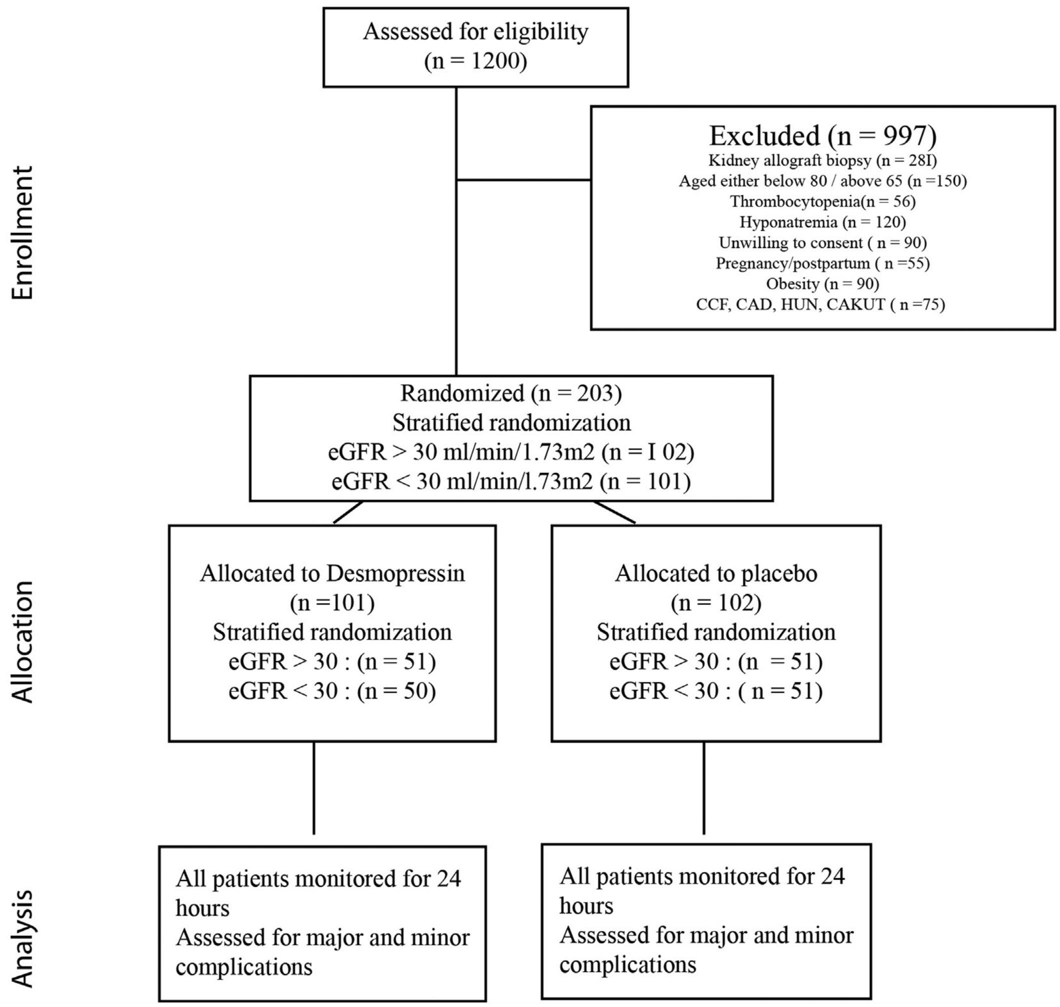

Figure 1. CONSORT diagram of the study.

numbers needed-to-treat for preventing 1 bleeding episode was 5.667.

Similarly, in the category of patients with eGFR < 30 ml/min per 1.73 m^2, the desmopressin group had a lower bleeding incidence (18%) than the placebo group (43.1%) ($P = 0.006$) (Table 3). The RR of bleeding in the desmopressin group was lower (RR: 0.42 [95% CI: 0.213–0.815], $P = 0.010$) than in the placebo patients. The numbers needed-to-treat for preventing 1 bleeding episode was 3.978. Further, stratification by varying degrees of renal function is presented in (Table 4).

Safety

Nasal discomfort after inhalation was observed in 78 patients (77.2%) in the desmopressin group and 84 (82.4%) in the placebo group. Hyponatremia was significantly more common in the desmopressin group (28.7%) than in the placebo group (5.8%) ($P < 0.001$). Nausea was observed in 2.9% of the patients in both arms. Headaches were also more frequent in the desmopressin group (7.9%) than in the placebo group (1.9%) ($P = 0.04$). Flushing and new onset rashes or itching were rare and showed no significant difference between the groups (Table 5). None of the patients had serious symptomatic hyponatremia or other serious adverse events. No patients died during the study.

Effect on Factor VIII and vWF With Desmopressin Levels

The changes in factor VIII and vWF level at 0, 2, and 4 hours are shown in Table 6 and Figure 2. Desmopressin significantly increased factor VIII and vWF levels at 2 hours compared with placebo (factor VIII: 20.4 ± 1.9 vs. 7.6 ± 0.71 ng/ml, vWF: 48.06 ± 5.3 vs, 25.83 ± 4.7 ng/ml; $P < 0.001$), but these effects diminish by 4 hours. There was no significant difference in reaction time, kinetic time, alpha angle, maximum amplitude, and lysis at 30 minutes after maximum amplitude between desmopressin and placebo groups (Table 1).

DISCUSSION

This study investigated the efficacy of desmopressin compared with placebo in reducing post–kidney biopsy

Table 1. Clinical and laboratory characteristics of the study population

Parameter	Total (N = 203)	Placebo (n = 102)	Desmopressin (n = 101)
Clinical profile			
Age (yrs), mean (SD)	40.60 (± 15.21)	42.64 (± 15.13)	38.53 (± 15.10)
Gender (male), n (%)	127 (62.56)	60 (58.82)	67 (66.33)
Diabetes mellitus, n (%)	27 (13.3)	13 (12.8)	14 (13.7)
Hypertension, n (%)	140 (68.9)	69 (67.6)	71 (70.3)
BMI (kg/m^2), mean (SD)	24.66 (± 6.51)	24.44 (± 5.19)	24.87 (± 7.63)
BP (systolic), mean (SD)[a]	117.87 (± 9.80)	118.00 (± 8.60)	118.76 (± 8.05)
BP (diastolic), mean (SD)[a]	77.17 (± 5.71)	77.89 (± 5.89)	76.44 (± 5.45)
Hb (g/dl), mean (SD)	10.53 (± 1.90)	10.30 (± 1.76)	10.73 (± 2.04)
TLC (× 10^3), mean (SD)	8.3 (± 3.46)	8.38 (± 3.27)	8.39 (± 3.67)
Platelet count (× 10^3), mean (SD)	204.51 (± 17.96)	207.45 (± 11.22)	201.54 (± 9.71)
PT (INR), mean (SD)	1.12 (± 0.79)	14.03 (± 2.10)	13.84 (± 1.30)
aPTT (s), mean (SD)	28.41 (± 3.46)	28.69 (± 3.32)	28.15 (± 3.60)
S creatinine (mg/dl), mean (SD)	2.40 (1.2,4.0)	2.47 (1.2,4.3)	2.40 (1.2, 3.8)
eGFR (ml/min per 1.73 m^2), median (IQR)	30 (16,71)	31 (14.7, 66.5)	30 (17.5, 73)
S sodium (mmol/l), mean (SD)	132.57 (± 6.78)	131.68 (± 6.85)	133.48 (± 6.76)
S Potassium (mmol/l), mean (SD)	4.26 (± 0.73)	4.17 (± 0.71)	4.43 (± 0.74)
S Protein (g/dl), mean (SD)	5.99 (± 1.32)	5.90 (± 1.50)	6.08 (± 1.13)
S albumin (g/dl), mean (SD)	3.28 (± 0.85)	3.31 (± 0.94)	3.26 (± 0.76)
eGFR category			
< 30 ml/min per 1.73 m^2, n (%)	101 (49.8)	51 (50)	50 (49.5)
>30 ml/min per 1.73m^2, n (%)	102 (50.2)	51 (50)	51 (50.5)
Clinical indication for biopsy			
Acute kidney injury, n (%)	21 (10.3)	11 (10.8)	10 (9.9)
RPRF, n (%)	46 (22.7)	25 (24.5)	21 (20.8)
Nephrotic syndrome, n (%)	78 (38.4)	38 (37.3)	40 (39.6)
Nephritic Syndrome, n (%)	15 (7.3)	7 (6.9)	8 (7.9)
CKD with normal kidney size, n (%)	15 (7.4)	6 (5.9)	9 (8.9)
Proteinuria, n (%)	28 (13.8)	15 (14.7)	13 (12.9)
Kidney biopsy			
Biopsy passes, mean (SD)	2.26 (± 0.46)	2.25 (± 0.47)	2.27 (± 0.46)
Number of glomeruli, median (IQR)	13.5 (10–15)	13 (9–15)	14 (10–16)
Biopsy diagnosis			
DGGS, n (%)	19 (6.5)	10 (9.8)	9 (8.9)
Crescentic GN, n (%)	32 (15.8)	15 (14.7)	17 (16.8)
MCD/ FSGS/MGN/MPGN/IgAN, n (%)	96 (47.3)	46 (45.09)	50 (49.5)
Lupus nephritis/amyloidosis (other secondary glomerular diseases)	25 (12.3)	13 (12.7)	12 (11.9)
ATN/AIN/ACN, n (%)	17 (8.37)	10 (9.8)	7 (6.9)
TMA, n (%)	5 (2.46)	3 (2.95)	2 (1.9)
Others, n (%)	9 (4.4)	4 (3.92)	5 (4.9)
Thromboelastographic parameters at baseline			
R time (minutes), median (IQR), min	5′32 (4′36–7′46)	5′38 (4′32–7′40)	5′29 (4′36–7′48)
K time (minutes), median (IQR)	1′58 (1′10–2′46)	1′50 (1′06–2′39)	1′59 (1′05–2′56)
Alpha angle (degrees), mean (SD)	71 (10)	69 (8.5)	72 (9.2)
LY 30 (%), mean (SD)	5 (1.2)	4.3 (1.5)	5.2 (1.4)
MA (mm), mean (SD)	60 (13)	57 (14)	62 (15)
Abnormal TEG[b], n (%)	18 (8.8)	9 (8.8)	9 (8.9)

ACN, acute cortical necrosis; AIN, acute interstitial nephritis; aPTT, activated partial thromboplastin time; ATN, acute tubular necrosis; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CKD, chronic kidney disease; DGGS, diffuse global glomerulosclerosis; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; Hb, hemoglobin; IgAN, IgA nephropathy; INR, international normalized ratio; IQR, interquartile range; K, potassium; K time, kinetic time (normal range: 1–3 min); LY 30, lysis at 30 min after MA (normal range: 0%–8%); MA, maximum amplitude (normal range; 51–69 mm); MCD, minimal change disease; MGN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; Na, sodium; PT, prothrombin time; R time, reaction time (normal range: 2–8 min); S, serum; TEG, thromboelastographic; TLC, total leucocyte count; TMA, thrombotic microangiopathy.

[a]Systolic and diastolic BP indicates the reading 5 minutes before administration of the drug or placebo.

[b]Abnormal TEG is considered when the observed value of either R time, K time, alpha angle, or MA is outside the recommended normal range. alpha angle, (normal range: 55–78 degrees).

bleeding and adverse complications. We observed that the incidence of post–kidney biopsy bleeding was significantly lower in the desmopressin group than in the placebo group, suggesting the potential of desmopressin in mitigating bleeding risk following kidney biopsy. However, previous studies have shown conflicting results. Manno *et al*.[9] reported similar results with desmopressin administered subcutaneously at

Table 2. Major and minor complications post–kidney biopsy

Parameter	Total ($N = 203$)	Placebo ($n = 102$)	Desmopressin ($n = 101$)	*P*-value
Bleeding, *n* (%)	46 (22.6)	34 (33.3)	12 (11.9)	0.0003
Hypotension, *n* (%)	15 (7.3)	11 (10.7)	4 (3.9)	0.061
Hb fall (> 1 g/dl), *n* (%)	49 (24.1)	18 (17.64)	31 (30.69)	0.031
PRBC transfusion, *n* (%)	8 (3.95)	3 (2.94)	5 (4.95)	0.461
Gross hematuria, *n* (%)	19 (9.4)	13 (12.7)	6 (5.9)	0.091
Hematoma, *n* (%)	43 (21.2)	31 (30.4)	12 (11.9)	0.001
Hematoma size (cm), mean (SD)[a]	2.96 (0.5)	3.51 (0.71)	2.12 (0.56)	0.010
Requirement of interventional radiological procedure – coiling or embolization, *n* (%)	2 (0.98)	1 (0.49)	1 (0.5)	0.990

Hb, hemoglobin; PRBC, packed red blood cell transfusion (minimum 1).
[a]Hematoma size as noted by the sonologist as the size of hematoma in its longest axis.

3 mg/kg 1 hour before biopsy compared with placebo with a lower RR (RR: 0.45; 95% CI: 0.24–0.85; $P = 0.01$) of bleeding in the desmopressin group, 13.7% as compared with 30.5% in the placebo group. However, they included only patients with creatinine < 1.5 mg/dl, a subpopulation with a low risk of bleeding because of lesser degrees of azotemia.[9] In addition, they noted a reduction of minor postbiopsy bleeding (hematoma < 2 cm) without any difference in major complications. The clinical relevance of reduction in minor biopsy bleeds in patients with eGFR > 60 ml/min per 1.73 m^2 who are already at low risk of bleeding is unclear. Our finding is also in concurrence with another RCT by Sattari *et al.*,[17] who found that desmopressin, when compared with placebo in patients with eGFR between 15 and 90 ml/min per 1.73 m^2 significantly reduced the risk of postbiopsy hematoma (40 % vs. 11.6%, $P < 0.05$) and a lesser volume of hematoma even if it occurs. A recent RCT from India by Sethi *et al.*[13] randomized 80 patients to either receive intranasal desmopressin 150 mg or placebo in patients with a mean eGFR of 20.82 ml/min per 1.73 m^2. They found no difference in major bleeding or requirement for intervention to control bleeding; however, they found a higher risk of postbiopsy hematoma (40% vs. 5%) and hematuria (17.5% vs. 2.5%) in those who received desmopressin. The logical explanation for such a paradoxical result while using a medication with proven hemostatic potential is unclear. It is possible that the dose given in the study was lower than that used in our study and possibly the required intranasal dose of desmopressin is higher, as used in our study, and patients may require 300 μg puff to obtain a therapeutic benefit, at which vWF is released. A retrospective study showed discordant results regarding creatinine levels and bleeding risk. For patients with creatinine levels < 1.8 mg/dl, there was an increase in bleeding incidents. In contrast, those with creatinine levels > 1.8 mg/dl experienced decreased bleeding.[12] The current study, by enrolling 203 patients and using the optimal dose of intranasal desmopressin, demonstrates that the benefit of desmopressin in preventing bleeding post–kidney biopsy is preserved in both eGFR groups, clarifying the doubts raised by these studies, which showed discordant results.[17]

It is well-known that with the decline in eGFR, the tendency to bleed increases and that a medication-reducing incidence of postbiopsy bleeding is crucial in patients with reduced eGFR. The present RCT reiterates the finding of our previous observational study, which showed a benefit of using desmopressin in patients with eGFR < 30 ml/min per 1.73 m^2.[8] However, in our previous study, more than half of these patients had received hemodialysis before biopsy, and the effect of hemodialysis on the reduction of biopsy bleeding has not been studied. The study was a retrospective analysis, with a tendency to use desmopressin in high-risk patients. The deleterious effect of receiving heparin, even in small doses during dialysis, on postbiopsy bleeding cannot be overlooked. One study by Sreedhara *et al.*[18] has shown that hemodialysis, even if heparin-free, may transiently worsen platelet aggregation, and this may be deleterious before kidney biopsy. Our current study included patients only if the procedure had been done 24 hours before the procedure and was strictly heparin-free. The

Table 3. Post–biopsy bleeding stratified according to eGFR

Parameter	Total ($N = 203$)			Placebo ($n = 102$)			Desmopressin ($n = 101$)			*P* value
Bleeding in "high" risk and "low risk" categories	N	B	(%)	N	B	(%)	N	B	(%)	
eGFR > 30 ml/min per 1.73 m^2, *n* (%)	102	15	14.7	51	12	23.5	51	3	5.9	0.010
eGFR < 30 ml/min per 1.73 m^2, *n* (%)	101	31	30.7	51	22	43.1	50	9	18	0.006

B, incidence of bleeding in subcategory; eGFR, estimated glomerular filtration rate; N, number randomized in the specific subcategory; %, percentage of randomized patients with bleeding in the specific subcategory (B/N × 100).

Table 4. Postbiopsy bleeding stratified into 5 groups of varying bleeding risk according to eGFR

	Total (N = 203)			Placebo (n = 102)			Desmopressin (n = 101)			
Parameter	N	B	(%)	N	B	(%)	N	B	(%)	P value
eGFR > 60 ml/min per 1.73 m^2, n (%)	43	4	9.3	22	3	13.6	21	1	4.76	0.321
eGFR: 45–59 ml/min per 1.73 m^2, n (%)	34	4	11.8	16	3	18.8	18	1	5.5	0.210
eGFR: 30–44 ml/min per 1.73 m^2, n (%)	25	7	28	14	6	42.9	11	1	9.1	0.062
eGFR: 15–29 ml/min per 1.73 m^2, n (%)	56	15	26.8	25	10	40	31	5	16.1	0.040
eGFR < 15 ml/min per 1.73 m^2, n (%)	45	16	35.6	25	12	48	20	4	20	0.050

B, incidence of bleeding in subcategory; eGFR, estimated glomerular filtration rate; N, number randomized in the specific subcategory; %, percentage of randomized patients with bleeding in the specific subcategory (B/N $\times$ 100).

optimal eGFR cut-off for initiating dialysis specifically to prevent postbiopsy bleeding remains unclear in the absence of other indications.

Our study is the first to demonstrate the levels of factor VIII and vWF, both prebiopsy and postbiopsy. The significant increase in factor VIII observed at 2 hours postbiopsy underscores the biological plausibility of using desmopressin. We also used TEG to analyze the baseline overall coagulation profiles with obvious intrinsic and extrinsic coagulation pathway abnormalities of study participants, which were similar in the desmopressin and placebo groups. Previous studies have compared TEG and bleeding time in predicting the risk of post–kidney biopsy bleeding and found that TEG had variable success in predicting the risk of bleeding in patients with renal dysfunction.[19] With regard to route of administration, desmopressin has been previously compared between i.v. and intranasal routes by Lethagen *et al*.[20] Intranasal desmopressin 300 μg was accurate, reproducible, and a convenient alternative to 0.2 μg/kg i.v. route. We chose intranasal route merely for the convenience of administration and these results may have been similar if corresponding i.v. routes had been used.

No major side effects were observed. A significant number of patients had asymptomatic hyponatremia, which was expected and deemed to be a transient effect because of the desmopressin effect. Although some studies quote the universal risk of hyponatremia and some quote severe hyponatremia, we did not find severe, worrisome, or persistent hyponatremia.[6] The therapeutic effect of desmopressin as a hemostatic agent is observed only when appropriate doses are used; and therefore, the high frequency of hyponatremia in our study could be a dose-dependent effect because we have used higher doses. Using lesser doses of the drug, such as 10 or 20 μg is unlikely to bring about desired clinical effects. The success rate in preventing bleeding was greater than that of previous reports in our study.[13] This may be because of the higher doses of desmopressin used in our study, a total of 300 μg (150 μg in each nostril), at which desmopressin works in patients with von Willebrand diseases. The higher percentage of hyponatremia and decrease in hemoglobin may again be because of this higher dose and more free water reabsorption from the distal convoluted tubules and collecting duct. The yield of kidney tissue in the study was not different between groups and was deemed adequate to diagnose most kidney diseases. There were no other notable side effects or study-related mortality.

The significant strengths of our study include its well-powered RCT design and is the only study that showed the changes in the level of factor VIII, and vWF in a time-dependent manner, which corroborates the drug's mechanistic relevance in addition to using appropriate dosing of intranasal desmopressin instead. This study also tested patients with thromboelastography before kidney biopsy to exclude any major abnormalities in extrinsic and intrinsic coagulation pathways. Limitations of this study include the lack of analysis on delayed biopsy bleeding because patients were not followed-up beyond index admission. However, all these patients were under the institute's follow-up for clinical care, and no such incident was reported to the trial investigators.

Table 5. Adverse effect of desmopressin and placebo

Parameter	Total (N = 203)	Placebo (n = 102)	Desmopressin (n = 101)	P value
Hyponatremia, n (%)	35 (17.2)	6 (5.8)	29 (28.7)	<0.001
Headache, n (%)	10 (4.9)	2 (1.9)	8 (7.9)	0.042
Flushing, n (%)	1 (0.49)	1 (0.99)	0	0.311
New onset rashes/itching, n (%)	1 (0.49)	1 (0.99)	0	0.317
Nausea/vomiting, n (%)	6 (2.9)	3 (2.9)	3 (2.9)	0.942
Nasal discomfort	162 (79.8)	84 (82.4)	78 (77.2)	0.357

Table 6. Effect of desmopressin on factor VIII, von Willebrand factor levels, and thromboelastography

Parameter	Placebo (n = 102)	Desmopressin (n = 101)	P value
Factor VIII (0 h), ng/ml	7.30 $\pm$ 0.87	7.43 $\pm$ 0.64	0.112
Factor VIII (2 h), ng/ml	8.60 $\pm$1.43	16.7 $\pm$ 2.26	<0.001
Factor VIII (4 h), ng/ml	8.14 $\pm$ 1.05	14.9 $\pm$ 1.82	<0.001
vWF (0 h), ng/ml	26.83 $\pm$ 6.93	26.06$\pm$ 6.44	0.410
vWF (2 h), ng/ml	26.21 $\pm$ 6.49	38.57$\pm$ 7.65	<0.001
vWF (4 h), ng/ml	26.32 $\pm$ 6.03	30.83 $\pm$ 6.9	<0.001

vWF, von Willebrand factor.

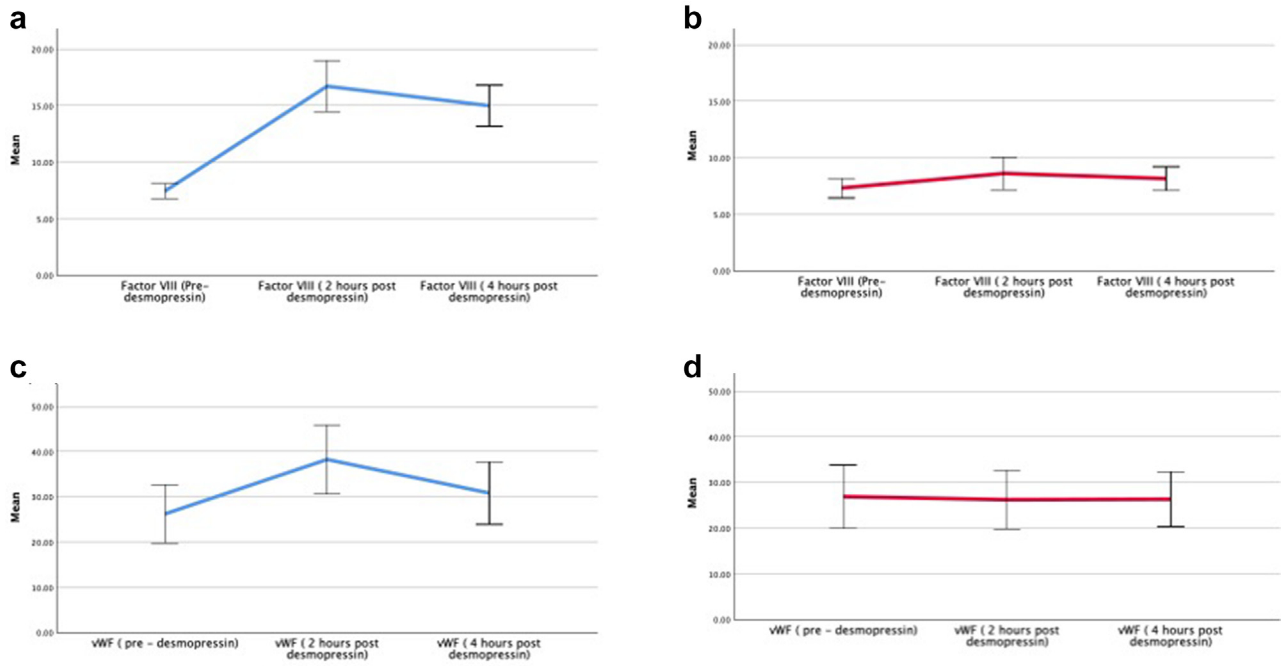

Figure 2. Line plot showing factor VIII and von Willebrand factor (vWF) levels in desmopressin and placebo arms at 0, 2, and 4 hours. (a) Factor VIII levels in patients who randomized to desmopressin at 0, 2, and 4 hours. (b) Factor VIII levels in patients randomized to placebo at 0, 2, and 4 hours. (c) von Willebrand factor levels in patients who randomized to desmopressin at 0, 2, and 4 hours. (d) von Willebrand factor levels in patients who randomized to placebo at 0, 2, and 4 hours. Simple means and errors bars with 95% CI $\pm$ 1 SD. CI, confidence interval.

Overall, the findings of this study support the potential clinical utility of desmopressin in reducing minor post–kidney biopsy bleeding and adverse complications, particularly among individuals with severely reduced eGFR. However, there was no difference in major complications. Future research could explore optimal dosing regimens and further evaluate desmopressin's safety and efficacy in diverse patient populations undergoing kidney biopsy. In addition, cost-effectiveness analyses may provide valuable insights into the economic implications of incorporating desmopressin into routine clinical practice for kidney biopsies, because 1 postbiopsy bleed prevention can be live and cost-saving, thus permitting clinicians to do high-risk biopsies safely.

DISCLOSURE

All the authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

The data are available with the study's principal investigators, and they can be made available upon reasonable request. The data cannot be public because of ethical issues and institute policy.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary information. Factor VIII and von Willebrand factor estimation by enzyme-linked immunosorbent assay technique.

Figure S1. Thromboelastography plot explaining the various parameters of clot formation and fibrinolysis.

Figure S2. Graph showing mean (SD) of the hemoglobin at various time points.

Table S1. Inclusion and exclusion criteria.

Table S2. A 2 x 2 factorial table for the primary outcome.

CONSORT Checklist.

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