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ORIGINAL ARTICLE

Intranasal desmopressin reduces renal biopsy-related bleeding and serum sodium levels in patients with reduced renal function

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ABSTRACT

Background: The use of desmopressin in preventing renal biopsy-related bleeding is not established and its effects on serum sodium levels are not well studied. The study aimed to compare the bleeding complication rates between the groups with and without desmopressin use prebiopsy and to observe the effect of desmopressin on postbiopsy serum sodium levels.

Methods: In this single-center, prospective and retrospective interventional study, from June 2018 onwards, patients with serum creatinine >132.6 μmol/L but not on dialysis and undergoing ultrasound-assisted needle-guided renal biopsy received 150 μg of desmopressin (D-amino D-arginine vasopressin (DDAVP)) (Group II). Data from patients from June 2017 to May 2018 were included in Group I in whom desmopressin was not used. Bleeding complications were monitored by clinical and ultrasound surveillance. Serum sodium levels were checked prior to and 24 h following desmopressin in Group II.

Results: A total of 194 patients were included in the study: 105 in Group I and 89 in Group II. Group II had lower overall minor bleeding complications and perinephric hematomas than Group I (15.7% versus 31.4%, 14% versus 27% and 7.8% versus 19% in Group II and Group I, respectively, with $P < 0.05$). Not using desmopressin and female sex were significant predictors for overall risk of bleeding on multivariate logistic regression. Serum sodium levels fell in 94% of patients in Group II. Lower prebiopsy serum sodium, higher estimated glomerular function rate and higher spot urine sodium values were associated with a greater decrease in serum sodium after desmopressin.

Conclusion: Intranasal desmopressin reduces bleeding complications during renal biopsies performed in patients with reduced renal function not requiring dialysis, albeit with a risk of developing hyponatremia.

Keywords: biopsy, bleeding, DDAVP, drug safety, hyponatremia

INTRODUCTION

Since its first description by Iversen and Brun [1], percutaneous renal biopsy has undergone several modifications that have added considerably to the general safety of the procedure, but the overall complication rates remain widely variable, from 1% to 25% [2, 3]. While minor complications cause only mild to no discomfort to the patient, major complications can cause significant morbidity and increased length of hospitalization and in rare cases, mortality as well. Therefore, over the years, several large studies have analyzed risk factors and compared techniques and operators, with the goal of minimizing biopsy-related

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bleeding complications [3–6]. Desmopressin, a vasopressin analogue used primarily in the treatment of diabetes insipidus, was evaluated clinically in the treatment of uremic bleeding in 1985, based on its effect of releasing factor VIII–von Willebrand factor (VWF) multimers in the circulation and shortening bleeding time [7]. However, the use of desmopressin prior to renal biopsy is supported by only one randomized controlled trial, which was done in patients at low risk of bleeding—those with a serum creatinine <132.4 μmol/L and/or an estimated glomerular function rate (eGFR) >60 mL/min/1.73 m^2 [8]. Even following this trial, desmopressin was not used universally in patients prior to renal biopsy, probably due to a lack of robust data supporting its use or pending issues related to its safety. A larger, multicenter, prospective and retrospective observational study by Peters *et al.* [9] compared bleeding complications between centers that did and did not administer desmopressin with their findings published in 2018. They reported that desmopressin reduces overall bleeding in patients with a serum creatinine >150 μmol/L, with a stronger effect in women than in men. This study did not look for effects of desmopressin on serum sodium levels and did not report any serious adverse effects.

Prior to 2018, our center followed a protocol of administering prebiopsy intranasal desmopressin to those patients who required hemodialysis prior to renal biopsy (typically those with a serum creatinine >442 μmol/L). Following the trial by Peters *et al.* [9], and our own data that showed higher bleeding complications with increasing serum creatinine, we changed our policy to start administering desmopressin to those with reduced renal function not requiring dialysis (whose serum creatinine was >132.4 μmol/L) [10]. This study was designed to compare bleeding complications in a homogeneous population, with a uniform ultrasound-guided renal biopsy procedure, operators and surveillance protocol for all patients, while monitoring for effects of desmopressin on serum sodium levels in the patients with reduced renal function not requiring dialysis. For this purpose, we retrieved our data for the previous year to provide for a comparison group with those patients receiving desmopressin.

MATERIALS AND METHODS

The study was conducted in a tertiary care referral hospital in India and was approved by the institute's ethical committee. A total of 194 patients were included in the study, 105 in Group I, the retrospective arm (June 2017–May 2018), and 89 in Group II, the prospective arm of the study (June 2018–April 2019). All patients whose serum creatinine was >132.4 μmol/L and/or eGFR was <60 mL/min/1.73 m^2 and not requiring hemodialysis were included in the analysis (eGFR was derived using the Chronic Kidney Disease Epidemiology Collaboration equation). Patients who required hemodialysis prior to biopsies were excluded, as by the institute's protocol. Also, patients with known cardiovascular disease, previous history of thrombotic events, prebiopsy serum sodium <125 mEq/L, transplant biopsies or those not providing informed consent were excluded.

All the patients were admitted prior to the procedure and underwent blood pressure measurements and routine investigations, including hemoglobin percentage, platelet count, coagulation profile, bleeding time, renal function tests and serum albumin levels, all of which were optimized prior to the procedure. For patients taking antiplatelet and anticoagulant drugs, these were stopped at least 2 weeks prior to the procedure after appropriate clearances. All the renal biopsies were done under real-time ultrasound guidance (Sono Site M-TURBO, Fujifilm Sonosite, Bothell, WA, USA) using the curvilinear 3.5-MHz probe, with an automated spring-loaded biopsy gun of 16 G or 18 G known as the BARD Max Core (Bard Peripheral Vascular, Tempe, AZ, USA) and a sterilized needle guide (Ultra-Pro II, CIVCO Medical Solutions, Coralville, IA, USA). Normally, two cores were taken using two to four passes in a tangential approach, by either of the two operators (both nephrologists). The biopsies were done in a prone position after surface cleaning with 2% povidone iodine and local anesthesia was provided using 10 mL of 2% lignocaine. All the patients underwent surveillance ultrasound immediately after the procedure to look for perinephric hematomas. The patients were followed up for 24 h postbiopsy to look for any symptoms and bleeding complications postprocedure.

In Group II, intranasal desmopressin was administered at a dose of 150 μg ~1 h prior to the planned renal biopsy. Patients with known cardiac disease or a history of thrombotic events in the past were excluded from the study. All the patients in Group II underwent prebiopsy serum sodium estimation along with other routine tests and those with serum sodium <125 mEq/L were excluded. In the postbiopsy period, repeat serum sodium and spot urine sodium estimation were performed 24 h after the biopsy. All the patients were instructed to restrict their fluid intakes to <1.5 L on the day of biopsy. Ultrasound surveillance and postbiopsy care remained the same in both periods.

Syndromic diagnoses were made according to widely used syndromes in nephrology practice. 'Nephrotic syndrome with renal dysfunction' was defined when features of nephrotic syndrome (proteinuria >3 g/24 h/1.73 m^2, hypoalbuminemia, edema and hyperlipidemia) were accompanied by reduced eGFR. 'Nephritic syndrome' was diagnosed based on a triad of oliguria, hypertension, edema and reduced eGFR. 'Rapidly progressive renal failure' was diagnosed when patients had a documented acute decrease in eGFR spanning days to weeks, with normal-sized kidneys. Major bleeding complications included the need for blood transfusion, digital subtraction angiography (with/without embolization) or cystoscopy. Minor complications included gross self-limited hematuria, symptomatic and asymptomatic perinephric hematomas and a hemoglobin decrease of >1 g/dL. Hemoglobin change was also recorded from blood samples taken pre- and 1-day postbiopsy.

Statistical analysis

The normality of data was tested using the Shapiro–Wilk test. The Mann–Whitney U-test was used to compare medians in case of non-normally distributed data and Student's *t*-test was used to compare means of normally distributed data. Categorical variables were compared using the Pearson's chi-square test. Logistic regression analysis was performed for analyzing predictors of biopsy-related bleeding complications. A P-value <0.05 was considered significant. Data analysis was done using SPSS software version 16.0 (SPSS, Chicago, IL, USA).

RESULTS

A total of 194 patients undergoing renal biopsies in the study period of 22 months who fulfilled the study criteria were included for analysis. The baseline demographic data of the study participants are presented in Table 1 and the histologic diagnoses on renal biopsies are presented in Table 2. Most of the clinical and laboratory parameters were comparable in the two groups, except slightly lower serum albumin levels in Group I.

Table 3 shows a comparison of complications (major, minor and overall) in the two groups. The incidence of perinephric

Table 1. Baseline clinical and laboratory characteristics of the study participants

Characteristics	Group I ($n = 105$)	Group II ($n = 89$)	P-value
Age (years)	36.0 ± 16.8	40.7 ± 16.8	0.271
Systolic blood pressure (mmHg)	129 ± 13	128 ± 13	0.831
Diastolic blood pressure (mmHg)	76 ± 8	76 ± 9	0.662
Hemoglobin (g/dL)	11.0 ± 2.2	11.4 ± 1.9	0.630
Platelet count ($\times 10^3/\mu L$)	250 ± 101	233 ± 103	0.866
Prothrombin time (s)	13.7 ± 1.5	13.4 ± 1.2	0.258
International normalized ratio	1.07 ± 0.16	1.03 ± 0.12	0.133
Activated partial thromboplastin time (s)	28.8 ± 2.3	28.0 ± 2.0	0.588
Bleeding time (s)	221 ± 35	229 ± 36	0.613
Serum creatinine (μmol/L)	216.5 ± 78.7	205.9 ± 83.1	0.399
eGFR (mL/min)	34.92 ± 14.58	36.58 ± 15.33	0.210
Serum albumin (g/dL)	2.31 ± 0.95	2.68 ± 1.12	0.020
Syndromic diagnosis, *n*			
Rapidly progressive renal failure	44	42	
Nephrotic syndrome with renal dysfunction	49	40	
Nephritic syndrome	12	7	
Kidney sizes by ultrasound (right/left) (cm)	10.0 ± 0.7/10.0 ± 0.7	9.9 ± 0.7/10.1 ± 0.7	0.86
Use of 16G biopsy needle (%)	83.8	79.7	0.312

Values presented as mean ± standard deviation unless stated otherwise.

Table 2. Biopsy diagnosis in the two groups

Group 1 ($n = 105$)	Group 2 ($n = 89$)
Acute tubulointerstitial nephritis (14)	Acute tubulointerstitial nephritis (10)
Diffuse global glomerulosclerosis (11)	Diffuse global glomerulosclerosis (6)
Diabetic nephropathy (3)	Diabetic nephropathy (4)
Focal segmental glomerulosclerosis (17)	Focal segmental glomerulosclerosis (10)
Hypertensive nephropathy (2)	Hypertensive nephropathy (2)
IgA nephropathy (14)	IgA nephropathy (12)
Infection-related glomerulonephritis (5)	Infection-related glomerulonephritis (8)
Lupus nephritis (6)	Lupus nephritis (4)
Minimal change disease (4)	Minimal change disease (13)
Membranous nephropathy (11)	Membranous nephropathy (6)
Membranoproliferative (including C3) glomerulonephritis (14)	Membranoproliferative (including C3) glomerulonephritis (10)
Pauci-immune glomerulonephritis (2)	Pauci-immune glomerulonephritis (2)
Renal amyloidosis (2)	Renal amyloidosis (2)

IgA, immunoglobulin A.

hematomas (of which 79% were asymptomatic and only three patients presented with symptoms of pain), self-limited gross hematuria and overall bleeding complications were significantly reduced in Group II, which received desmopressin. Major complications were not significantly different in the two groups. The overall bleeding complication rate was 24.2%, with major complications occurring in 2% and minor complications, including asymptomatic perinephric hematomas, accounting for the rest. Hemoglobin change from the pre- to postbiopsy period did not vary significantly between the two groups, nor did the length of hospital stay. Table 4 shows the predictors of bleeding complications. On performing univariate logistic regression analysis, lower prebiopsy hemoglobin, female sex, lower eGFR and not using desmopressin were associated with a higher risk of bleeding complications. A model consisting of two variables, female sex and the use of desmopressin, could explain 12% of the variance in the occurrence of bleeding complications and incorrectly classified 76% of the cases.

Patients in Group II also underwent pre- and postbiopsy serum sodium estimation to study the effect of intranasal desmopressin on serum sodium levels in patients with varying renal function and undergoing renal biopsies. Table 5 showed that besides eGFR, prebiopsy serum sodium and spot urine sodium levels were significantly associated with a greater decrease in serum sodium after desmopressin administration. The maximum decrease in serum sodium was 13 mEq/L and the minimum was 118 mEq/L, with 94% of patients showing a decrease in serum sodium after desmopressin. The mean decrease in serum sodium was 4.36 mEq/L. None of the patients showed any symptoms associated with acute hyponatremia and eight patients with serum sodium levels <130 mEq/L (only one had serum sodium <125 mEq/L) were observed for an extra day in the hospital, and all showed recovery of serum sodium levels with fluid restriction alone for >24 h. With regard to coadministered drugs that could contribute to a decrease in serum sodium levels, concomitant administration of loop diuretic (furosemide/torsemide) took place in 54%, mineralocorticoid antagonist spironolactone in 17% and renin–angiotensin system (RAS) inhibitors (ramipril, losartan, telmisartan) in 12% of Group II. None of the drugs, either alone or in combination, were found to correlate significantly with postbiopsy serum sodium decrease.

Table 3. Bleeding complications in the study population

Complications	Group I ($n = 105$)	Group II ($n = 89$)	P-value
Perinephric hematoma, *n* (%)	19 (18)	7 (7.8)	0.02
Gross hematuria (self-limited), *n* (%)	14 (13.4)	7 (7.8)	0.03
Need for blood transfusion, *n* (%)	4 (3.8)	0 (0)	0.15
Need for digital substraction angiography, *n* (%)	1 (0.9)	0 (0)	0.10
Cystoscopy, *n* (%)	0 (0)	0 (0)	
Hemoglobin change (g/dL) mean ± SD	0.0 ± 0.7	0.2 ± 0.7	0.64
Overall bleeding complications, *n* (%)	33 (31.4)	14 (15.7)	0.01
Length of hospital stay (days) mean ± SD	4.9 ± 3.5	4.5 ± 3.8	0.80

SD, standard deviation.

Table 4. Predictors of bleeding complications in the study population

Variable	P-value	Odds ratio (95% CI)
Univariate logistic regression		
Prebiopsy hemoglobin	0.027	1.218 (1.02–1.45)
Female sex	0.000	4.131 (2.07–8.25)
Use of desmopressin	0.012	2.450 (1.21–4.96)
eGFR	0.052	1.080 (0.88–1.11)
Multivariate logistic regression		
Female sex	0.000	4.41 (2.17–8.97)
Use of desmopressin	0.037	2.19 (1.05–4.58)

CI, confidence interval.

Table 5. Predictors of a decrease in serum sodium after desmopressin use in the study population (Group II)

Variable	R-value	P-value
eGFR	0.202	0.051
Prebiopsy serum sodium	0.343	0.001
Spot urinary sodium	0.377	0.020

DISCUSSION

This study indicates that the use of intranasal desmopressin is associated with lower overall bleeding complications and minor complications, including perinephric hematomas, in patients with serum creatinine >132.4 μmol/L but not requiring dialysis. Major complications were also fewer, although the difference did not reach statistical significance. The data on the efficacy of using desmopressin for the prevention of biopsy-related bleeding come primarily from two studies. Manno *et al.* [8] performed a single-center, randomized controlled trial with a total of 162 patients, where only patients with serum creatinine <132.4 μmol/L were included, and desmopressin demonstrated efficacy in reducing postbiopsy bleeding (mainly minor complications in terms of the number and size of perinephric hematomas). In contrast, Peters *et al.* [9] published their multicenter observational study in 2018, where one center with prebiopsy desmopressin use (at a serum creatinine >150 μmol/L) was compared with other centers where desmopressin was not used. They demonstrated fewer overall complications with the use of desmopressin, with no statistically significant difference in the rates of major and minor bleeding complications.

The study by Manno *et al.* [8] established the efficacy of desmopressin in preventing biopsy-related bleeding in patients who were at low risk of bleeding—those with serum creatinine <132.4 μmol/L and/or eGFR >60 mL/min/1.73 m^2. Their argument was that it was unethical to withhold desmopressin for patients with deranged renal function prior to renal biopsy. Their assertion was based on the classic paper by Mannucci *et al.* [7], who noted shortening of bleeding times and the appearance of larger factor VIII–VWF multimers in the plasma of 12 dialysis-dependent patients with coexisting bleeding problems, and also noted no undue blood losses in 6 other patients undergoing renal biopsies. However, the use of desmopressin in those with serum creatinine >132.4 μmol/L is not universal and no guidelines for its use exist in the literature. Many centers still do not practice desmopressin administration prior to renal biopsies in all patients with serum creatinine >132.4 μmol/L, as is evident from the Peters *et al.* [9] study and our previous study. While the study by Peters *et al.* showed the efficacy of desmopressin in high-risk patients, it could not convincingly demonstrate any effect on either major or minor complications, probably since the occurrence of asymptomatic perinephric hematomas was not being monitored per protocol. Asymptomatic perinephric hematomas occur in about a quarter of all percutaneous renal biopsies and can only be picked up by ultrasound surveillance and/or a decrease in hemoglobin postbiopsy [11]. Similar to the study by Manno *et al.* [8], we also found a reduction in the occurrence of hematomas as well as minor complications after desmopressin. In those patients who require hemodialysis, it is difficult to separately assess the effects of hemodialysis and desmopressin in the prevention of bleeding complications. Therefore, for our study, we excluded dialysis-requiring patients from the analysis. In this set of patients with serum creatinine >132.4 μmol/L but not requiring hemodialysis, female sex, lower prebiopsy hemoglobin, lower eGFR and not using desmopressin predicted the development of bleeding complications as well as the occurrence of perinephric hematomas.

Anandagoda *et al.* [12] questioned the safety of prebiopsy desmopressin in their case report involving a postrenal transplant patient who developed hyponatremic seizures after desmopressin and later recovered after sodium correction. The dose of intranasal and subcutaneous desmopressin given prior to renal biopsies is higher than the dose administered in the treatment of neurogenic diabetes insipidus. Therefore it comes as no surprise that the decrease in serum sodium values was nearly universal (>90%) in our study. The finding of a positive correlation between a decrease in serum sodium values and eGFR is theoretically plausible, as vasopressin-induced water retention requires intact tubular function, which is progressively lost with decreasing GFR. In this study, lower prebiopsy serum sodium values were associated with a greater decrease in sodium levels secondary to desmopressin use. This finding

could alert clinicians to adopt more meticulous fluid restriction and sodium monitoring strategies for patients with lower serum sodium levels (in the range of 131–135 mEq/L) prior to biopsy. A high spot urine sodium value (>20 mEq/L) is indicative of vasopressin action on distal tubules and collecting ducts and can therefore be considered an ancillary finding in patients at a higher risk of hyponatremia [13]. Loop diuretics are commonly prescribed in patients with edema secondary to nephrotic state and renal dysfunction, and they can precipitate hypovolemic hyponatremia in these individuals. Spironolactone and RAS inhibitors with their antimineralocorticoid effects also lead to sodium losses. Theoretically, a combination of diuretics or RAS inhibitors and desmopressin, with their combined effects of salt wasting and water conservation, should precipitate hyponatremia; however, this study did not find any positive association between the use of these drugs and the development of hyponatremia. One reason could be due to gating or breaking effects due to the continued use of diuretics or intrinsic tubular resistance due to the effects of these drugs. Nevertheless, as the dose and duration of diuretics and RAS inhibitors were not standardized for all the patients, a role for these drugs in the subsequent development of hyponatremia cannot be denied based on this study. The other limitations of the study include its single-center design, partly retrospective data collection, lack of post-biopsy serum sodium levels in Group I and lack of information on oral fluid intake in Group II.

CONCLUSION

In patients with renal dysfunction not requiring hemodialysis, desmopressin reduces overall renal biopsy-related bleeding complications, especially minor complications such as perinephric hematomas. However, the use of desmopressin is associated with anasymptomatic decrease in serum sodium concentrations, more so in patients with preexisting low serum sodium levels.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Iversen P, Brun C. Aspiration biopsy of the kidney. *Am J Med* 1951; 11: 324–330
2. Hogan JJ, Mocanu M, Berns JS. The native kidney biopsy: update and evidence for best practice. *Clin J Am Soc Nephrol* 2016; 11: 354–362
3. Corapi KM, Chen JL, Balk EM *et al*. Bleeding complications of native kidney biopsy: a systematic review and meta-analysis. *Am J Kidney Dis* 2012; 60: 62–73
4. Tondel C, Vikse BE, Bostad L *et al*. Safety and complications of percutaneous kidney biopsies in 715 children and 8573 adults in Norway. *Clin J Am Soc Nephrol* 2012; 7: 1591–1597
5. Gupta RK, Balogun RA. Native renal biopsies: complications and glomerular yield between radiologists and nephrologists. *J Nephrol* 2005; 18: 553–558
6. Manno C, Strippoli GF, Arnesano L *et al*. Predictors of bleeding complications in percutaneous ultrasound-guided renal biopsy. *Kidney Int* 2004; 66: 1570–1577
7. Mannucci PM, Remuzzi G, Pusineri F *et al*. Deamino-8-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med* 1983; 308: 8–12
8. Manno C, Bonifati C, Torres DD *et al*. Desmopressin acetate in percutaneous ultrasound-guided kidney biopsy: a randomized controlled trial. *Am J Kidney Dis* 2011; 57: 850–855
9. Peters B, Hadimeri H, Mölne J *et al*. Desmopressin (Octostim®) before a native kidney biopsy can reduce the risk for biopsy complications in patients with impaired renal function: a pilot study. *Nephrology (Carlton)* 2018; 23: 366–370
10. Rao NS, Chandra A. Needle guides enhance tissue adequacy and safety of ultrasound-guided renal biopsies. *Kidney Res Clin Pract* 2018; 37: 41–48
11. Ishikawa E, Nomura S, Hamaguchi T *et al*. Ultrasonography as a predictor of overt bleeding after renal biopsy. *Clin Exp Nephrol* 2009; 13: 325–331
12. Anandagoda N, Jayawardene S, Macdougall IC *et al*. Desmopressin use prior to renal transplant biopsy—does it fit? *Clin Kidney J* 2014; 7: 602–604
13. Decaux G, Musch W. Clinical laboratory evaluation of the syndrome of inappropriate secretion of antidiuretic hormone. *Clin J Am Soc Nephrol* 2008; 3: 1175–1184

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