Bleeding Complications and Adverse Events After Desmopressin Acetate for Percutaneous Renal Transplant Biopsy

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Original Article

Abstract

Introduction: Percutaneous renal biopsy remains critical for the workup of renal allograft dysfunction but is associated with the risk of bleeding. Prophylactic intravenous desmopressin has been proposed to reduce bleeding risk in native renal biopsies, but its efficacy in the renal transplant population is unclear and adverse events such as severe hyponatraemia have been reported. Materials and Methods: We conducted a single-centre retrospective cohort study involving adult (≥21 years old) renal transplant recipients with impaired renal function (serum creatinine ≥150 µmol/L) who underwent ultrasound-guided renal allograft biopsies from 2011–2015 to investigate the effect of prebiopsy desmopressin on the risk of bleeding and adverse events. Results: Desmopressin was administered to 98 of 195 cases who had lower renal function, lower haemoglobin and more diuretic use. Postbiopsy bleeding was not significantly different between the 2 groups (adjusted odds ratio [OR] 0.79, 95% confidence interval [CI] 0.26–2.43, \( P = 0.68 \)) but desmopressin increased the risk of postbiopsy hyponatraemia (sodium [Na] <135 mmol/L) (adjusted OR 2.24, 95% CI 1.10–4.59, \( P = 0.03 \)). Seven cases of severe hyponatraemia (Na <125 mmol/L) developed in the desmopressin group, while none did in the non-desmopressin group. Amongst those who received desmopressin, risk of hyponatraemia was lower (OR 0.26, 95% CI 0.09–0.72, \( P = 0.01 \)) if fluid intake was <1 L on the day of biopsy. Conclusion: Prophylactic desmopressin for renal allograft biopsy may be associated with significant hyponatraemia but its effect on bleeding risk is unclear. Fluid restriction (where feasible) should be recommended when desmopressin is used during renal allograft biopsy. A randomised controlled trial is needed to clarify these outcomes.

Key words: Adverse effects, Deamino arginine vasopressin, Haematoma, Haemorrhage, Hyponatraemia

Introduction

Renal allograft biopsy remains critical for the diagnosis and management of renal dysfunction amongst renal transplant recipients but is associated with the risk of complications.1–5 Bleeding complications include gross haematuria and perinephric haematoma which may lead to urinary tract obstruction,6 Page kidney,7 blood transfusions, bladder irrigation, radiological, cystoscopic or surgical interventions,2 increased length of hospitalisation,8,9 graft loss and even death.10 Treatment for these complications may be associated with further adverse events such as allo-sensitisation (with blood transfusions)11 and contrast-induced nephropathy (with the use of iodinated contrast).

The reported risk of bleeding complications after renal allograft biopsy from previous studies is 1.8–10.3%.2,6,10,12–14 Desmopressin acetate, otherwise known as 1-Deamino-8-D-Arginine Vasopressin (DDAVP), has been shown to reduce bleeding complications in native renal biopsies of patients with both normal15 and impaired renal function.16 However, its efficacy is unclear for renal allograft biopsies and severe hyponatraemia has been reported.17 Other previously reported adverse effects of DDAVP include thrombotic events such as acute myocardial infarctions18,19 and minor effects such as headache, flushing and diarrhoea.20,21

We sought to investigate the effect of prebiopsy single-dose intravenous DDAVP on the risk of postbiopsy bleeding.
and severe adverse events such as hyponatraemia and thrombotic events in our renal transplant recipients with impaired renal function who underwent ultrasound-guided percutaneous allograft biopsies.

Materials and Methods

Study Design

We performed a retrospective chart review of all percutaneous renal allograft biopsies in adult (≥21 years old) renal transplant recipients with impaired renal function (serum creatinine ≥150 μmol/L) in the Singapore General Hospital between 2011–2015. Singapore General Hospital is a tertiary academic centre and is 1 of 2 transplant centres in Singapore, with >800 renal transplant recipients on active follow-up. Patients were identified from a procedure log of renal biopsies performed by nephrologists and interventional radiologists.

All biopsies were performed based on clinical indications. Patients were routinely admitted and observed for at least 24 hours post-biopsy. Baseline renal function, electrolytes, full blood count and coagulation profile with activated partial thromboplastin time (aPTT) and prothrombin time (PT) were performed within 3 days prior to renal biopsy. Relative contraindications for biopsy include systolic blood pressure >160 mmHg and use of antiplatelets or anticoagulants.

DDAVP was administered as a single intravenous dose within an hour before biopsy. The recommended dose of DDAVP in our institution is 0.3 μg/kg. Its use was left to the discretion of individual physicians but was suggested if patients had serum urea >15 mmol/L, serum creatinine >200 μmol/L or estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m².

All biopsies were performed under direct ultrasound guidance using a 16-gauge automated spring-loaded gun (Bard® Magnum® Reusable Core Biopsy System, Bard Biopsy Systems, United States; or BioPince™ Full Core Biopsy Instrument, Argon Medical Devices, United States). Adequacy of samples was confirmed immediately by a trained laboratory technician using light microscopy. Following the biopsy, patients were instructed to lie supine for at least 6 hours and observed for at least 24 hours. Repeat investigations such as blood count, electrolytes, including serum sodium, and imaging of the renal allograft were not routine and were repeated based on clinical indications.

Outcomes and Measurements

The primary outcome was post-biopsy bleeding. Bleeding complications were classified (similar to previous studies) as minor bleeding—defined as gross haematuria or radiologically-confirmed perinephric haematoma not requiring intervention—and major bleeding—defined as need for blood transfusion, bladder irrigation, radiological, cystoscopic or surgical intervention or death. Secondary outcomes were hyponatraemia and thrombotic events. Hyponatraemia and severe hyponatraemia were defined by serum sodium <135 mmol/L and <125 mmol/L, respectively, within 3 days post-biopsy. The half-life of DDAVP is found to be 2–3 times longer in patients with renal impairment and its effect on urine osmolarity can last up to 48 hours. As such, we selected 3 days as the cutoff for the detection of hyponatraemia in our study. Thrombotic events were defined as any thrombotic events that occurred within 2 weeks post-biopsy including acute myocardial infarction, deep vein thrombosis, pulmonary embolism, arteriovenous fistula, graft thrombosis or renal artery or vein thrombosis.

The following data were retrieved from electronic medical records: patient demographic, cause of end-stage renal disease (ESRD), transplant characteristics (e.g. type and vintage of transplant, maintenance immunosuppression), comorbidities, fluid intake on the day of biopsy, laboratory values (e.g. pre-biopsy haemoglobin, PT, aPTT, platelet, serum sodium, urea, creatinine, urine protein-to-creatinine ratio) within 3 days before biopsy and medications that may affect risk of bleeding (e.g. DDAVP, antiplatelets, anticoagulants) or hyponatraemia (e.g. diuretics, intravenous immunoglobulins, opioids, non-steroidal anti-inflammatory drugs, antiepileptics, antidepressants, antipsychotics, co-trimoxazole, ciprofloxacin) within 2 weeks of biopsy. All laboratory investigations were performed in the central laboratory which is accredited by the College of American Pathologists. eGFR was calculated using the Modification of Diet in Renal Disease equation.

Statistical Analysis

Results are expressed as median and interquartile range (25th and 75th percentiles) for continuous data and as frequency and percentage for categorical data. Mann-Whitney U test was used to compare continuous variables while Pearson chi-square test or Fisher’s Exact test was used for categorical variables. Univariable and multivariable logistic regression were performed to estimate the odds ratio (OR) and adjusted OR, respectively, for each risk factor of bleeding and hyponatraemia. Factors with P < 0.10 on univariable analysis were selected for multivariate analysis. All analyses were performed using SPSS for Windows (release 17.0) and R version 3.5.1; 2-sided P < 0.05 was considered statistically significant.

Ethics Approval

This study abided by the Declaration of Helsinki and waiver of informed consent for this retrospective electronic chart review.
medical records review was approved by the local institutional review board (CIRBE 2017/2647).

**Results**

We performed 195 renal allograft biopsies in 142 patients from June 2011 to July 2015. Ninety-eight biopsies were performed with prebiopsy intravenous DDAVP (DDAVP group) and 97 without (non-DDAVP group). No cases were lost to follow-up.

Baseline characteristics of both groups are listed in Table 1. The DDAVP group had worse renal function, lower prebiopsy haemoglobin and a higher proportion of loop diuretic use.

**Bleeding**

The rates of bleeding complications are summarised in Table 2. Incidence of overall, major and minor bleeding were not different between biopsies with and without DDAVP prophylaxis. Additional adjustment for eGFR still showed that DDAVP use did not significantly impact bleeding risk (adjusted OR 0.79, 95% confidence interval [CI] 0.26–2.43, \( P = 0.68 \)).

Other factors found to be significantly associated with overall bleeding complications include prebiopsy haemoglobin <8 g/dL (OR 6.30, 95% CI 1.69–23.5, \( P = 0.006 \)), platelets <200 × 10^9/L (OR 3.48, 95% CI 1.21–10.0, \( P = 0.02 \)) and diabetes mellitus as the cause of ESRD (OR 10.16, 95% CI 2.58–38.96, \( P = 0.001 \)). DDAVP did not significantly alter the bleeding risk even with adjustment for each of these risk factors. Conversely, lower haemoglobin and platelet count and diabetes as the causes of ESRD remained significantly associated with bleeding after adjustment for DDAVP (see Supplementary Tables 1 and 2).

**DDAVP-Related Adverse Events**

Almost all cases (\( n = 177 \), 90.8%) had serum sodium repeated within 3 days after biopsy. Table 2 shows that those administered DDAVP were more likely to have

| Variable                              | DDAVP (n = 98) | Non-DDAVP (n = 97) | \( P \) Value |
|---------------------------------------|---------------|--------------------|---------------|
| Age, years (IQR)                      | 50.6 (15.3)   | 50.6 (13.8)        | 0.81          |
| Male, n (%)                           | 51 (52.0)     | 58 (59.8)          | 0.31          |
| Ethnicity, n (%)                      |               |                    | 0.63          |
| Chinese                               | 61 (62.2)     | 68 (70.1)          |               |
| Malay                                 | 23 (23.5)     | 19 (19.6)          |               |
| Indian                                | 10 (10.2)     | 6 (6.2)            |               |
| Others                                | 4 (4.1)       | 4 (4.1)            |               |
| Renal disease and transplant character |               |                    | 0.10          |
| Cause of ESRD, n (%)                  |               |                    |               |
| Glomerulonephritis                    | 64 (65.3)     | 73 (75.3)          |               |
| Hypertension                          | 9 (9.2)       | 4 (4.1)            |               |
| Diabetes mellitus                     | 4 (4.1)       | 8 (8.2)            |               |
| Others/unknown                        | 21 (21.4)     | 12 (12.4)          |               |
| Type of transplant, n (%)             |               |                    | 0.10          |
| Living donor                          | 30 (31.3)     | 42 (43.3)          |               |
| Deceased donor                        | 66 (68.8)     | 55 (56.7)          |               |
| Years since transplant (IQR)          | 5.35 (11.63)  | 3.68 (8.22)        | 0.33          |
| Maintenance immunosuppression, n (%)  |               |                    |               |
| Prednisolone                          | 97 (99.0)     | 96 (99.0)          | 1.00          |
| Tacrolimus                            | 45 (45.9)     | 51 (52.6)          | 0.39          |
| Cyclosporin A                         | 43 (43.9)     | 38 (39.2)          | 0.56          |
| Mycophenolate                         | 74 (75.5)     | 80 (82.5)          | 0.29          |
| Azathioprine                          | 6 (6.1)       | 6 (6.2)            | 1.00          |
| Everolimus                            | 10 (10.2)     | 5 (5.2)            | 0.28          |
| Sirolimus                             | 3 (3.1)       | 4 (4.1)            | 0.72          |

DDAVP: Desmopressin acetate; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; IQR: Interquartile range; NA: Not applicable
hyponatraemia and had a greater drop in serum sodium. In multivariable modelling (Table 3), DDAVP remained independently associated with postbiopsy hyponatraemia (adjusted OR 2.73, 95% CI 1.20–6.22, *P* = 0.02) after adjustment for eGFR, prebiopsy sodium, fluid intake on day of biopsy, diuretics, intravenous immunoglobulin (IVIG) use and type of renal transplant. Seven cases in the DDAVP group developed severe hyponatraemia while none did in the non-DDAVP group (see Supplementary Tables 3 and 4). Amongst the cases of severe hyponatraemia, 1 developed mild symptoms requiring correction with 3% sodium chloride, while another developed seizures and required high dependency ward admission and 3% sodium chloride infusion.
Table 2. Postbiopsy Bleeding and Adverse Events According to Prebiopsy Desmopressin Acetate Administration

| Variable                                           | DDA VP (n = 98) | Non-DDA VP (n = 97) | P Value |
|----------------------------------------------------|-----------------|---------------------|---------|
| Overall bleeding complications, n (%)              | 8 (8.2)         | 8 (8.2)             | 1.00    |
| Minor bleeding complications, n (%)                | 6 (6.1)         | 8 (8.2)             | 0.59    |
| Gross haematuria, n (%)                            | 5 (5.1)         | 3 (3.1)             | 0.72    |
| Radiologically-confirmed perinephric haematoma, n (%)| 1 (1.0)         | 6 (6.2)             | 0.12    |
| Major bleeding complications, n (%)                | 5 (5.1)         | 2 (2.1)             | 0.45    |
| Blood transfusion, n (%)                           | 4 (4.1)         | 1 (1.0)             | 0.37    |
| Bladder irrigation, n (%)                          | 2 (2.0)         | 1 (1.0)             | 1.00    |
| Cystoscopy, n (%)                                  | 0 (0.0)         | 0 (0.0)             | NA      |
| Radiological intervention, n (%)                   | 1 (1.0)         | 0 (0.0)             | NA      |
| Surgery, n (%)                                     | 0 (0.0)         | 0 (0.0)             | NA      |
| Death, n (%)                                       | 0 (0.0)         | 0 (0.0)             | NA      |
| Adverse events                                     |                 |                     |         |
| Hyponatraemia, n (%)                               | 43 (46.7)       | 27 (31.8)           | 0.047   |
| Severe hyponatraemia, n (%)                        | 7 (7.6)         | 0 (0.0)             | NA      |
| Change in serum sodium, mmol/L (IQR)              | -4.0 (5.0)      | -1.0 (5.0)          | <0.001  |
| Thrombotic events, n (%)                           | 0 (0.0)         | 0 (0.0)             | NA      |

DDAVP: Desmopressin acetate; IQR: Interquartile range; NA: Not applicable

Table 3. Risk Factors for Hyponatraemia

| Variable                                           | Univariable Model | Multivariable Model |
|----------------------------------------------------|-------------------|---------------------|
|                                                    | OR                | 95% CI              | P Value | Adjusted OR | 95% CI          | P Value |
| DDAVP use                                          | 1.89              | 1.02 – 3.48         | 0.04    | 3.20        | 1.35 – 7.57     | 0.008   |
| eGFR, per mL/min/1.73 m² increment                 | 0.99              | 0.96 – 1.02         | 0.42    | 0.97        | 0.93 – 1.01     | 0.11    |
| Prebiopsy serum sodium, per mmol/L increment      | 0.75              | 0.66 – 0.85         | <0.001  | 0.73        | 0.63 – 0.85     | <0.001  |
| Fluid intake, per 100 mL increment                 | 1.06              | 1.00 – 1.08         | 0.03    | 1.06        | 1.01 – 1.11     | 0.01    |
| Diuretic use                                       | 0.54              | 0.27 – 1.05         | 0.07    | 0.46        | 0.20 – 1.05     | 0.07    |
| IVIG use                                           | 3.85              | 0.96 – 15.44        | 0.06    | 5.34        | 1.01 – 28.21    | 0.048   |
| DDRT (vs LDRT)                                     | 0.50              | 0.27 – 0.93         | 0.03    | 0.55        | 0.25 – 1.18     | 0.12    |

CI: Confidence interval; DDAVP: Desmopressin acetate; DDRT: Deceased donor renal transplant; eGFR: Estimated glomerular filtration rate; IVIG: Intravenous immunoglobulin; LDRT: Living donor renal transplant; OR: Odds ratio

DDAVP was used in 10 of 25 cases with prebiopsy hyponatraemia and resulted in a greater reduction in postbiopsy serum sodium compared to those without DDAVP (-7.0 mmol/L vs +1.0 mmol/L, P = 0.03). After excluding cases with prebiopsy hyponatraemia, DDAVP remained significantly associated with postbiopsy hyponatraemia (43.5% vs 23.9%, OR 2.45, 95% CI 1.22–4.90, P = 0.01).

Medications associated with hyponatraemia such as opioids (n = 26), co-trimoxazole (n = 14), omeprazole (n = 16), IVIG (n = 10), ciprofloxacin (n = 6) and haloperidol (n = 1) were administered within 2 weeks prior to biopsy in 42 cases. Antidepressants, antiepileptics or non-steroidal anti-inflammatory drugs were not used. These medications were not associated with postbiopsy hyponatraemia and exclusion of these 42 cases did not alter the association between DDAVP and hyponatraemia (46.5% vs 28.8%, OR 2.15, 95% CI 1.06–4.31, P = 0.04). No thrombotic events were detected in our study.

**DDAVP Subgroup**

Among the 98 cases who received DDAVP, higher fluid intake was associated with hyponatraemia (adjusted OR 1.22 per 100 mL increment, 95% CI 1.10–1.36, P <0.001), while diuretic use (adjusted OR 0.28, 95% CI 0.09–0.86, P = 0.03) and higher prebiopsy sodium (adjusted OR 0.58 per 1 mmol/L increment, 95% CI 0.42–0.79, P <0.001) were
protective. Those who developed hyponatraemia had lower median prebiopsy sodium (137 mmol/L vs 139 mmol/L, \( P < 0.001 \)) and higher median biopsy day fluid intake (1717 mL vs 1100 mL, \( P = 0.001 \)). Risk of hyponatraemia was lower (OR 0.26, 95% CI 0.09–0.72, \( P = 0.01 \)) and cases of severe hyponatraemia was absent among those with fluid intake of <1 L on the day of biopsy.

**Discussion**

Our study suggests that prebiopsy intravenous DDAVP for percutaneous renal allograft biopsy may increase the risk of hyponatraemia but may not alter the risk of bleeding.

While the use of DDAVP to reduce the risk of bleeding during renal allograft biopsies was previously reported (Table 4), there were no previous studies investigating its efficacy and safety in the renal transplant population. The only randomised controlled trial (RCT)\(^\text{15}^\) included only native renal biopsies in patients with normal renal function (eGFR ≥60 mL/min/1.73 m\(^2\)) and suggested that DDAVP can reduce the development of peri-nephric haematomas. The study also showed that DDAVP reduced the size of haematomas and length of hospitalisation but had no effect on the risk of major complications (i.e. the development of arteriovenous fistulas, need for angiography, embolisation or surgery). A recent pilot retrospective study\(^\text{16}^\) with multi-centre registry data showed that DDAVP prior to native renal biopsies reduces the risk of overall and major complications in patients with serum creatinine of >150 µmol/L. Another study has further supported that the beneficial effect of DDAVP may be greater in patients with worse renal function.\(^\text{26}^\)

The mechanism by which DDAVP might reduce the risk of bleeding in the setting of renal impairment is not exactly understood. DDAVP increases circulating levels of von Willebrand factor and factor VIII and enhances platelet adhesion.\(^\text{27}^\) Several studies demonstrated that DDAVP reduces bleeding time in patients with renal impairment.\(^\text{28–30}^\) However, more recent studies have also found that bleeding

### Table 4. Previously Reported Use of DDAVP for Renal Allograft Biopsy

| Authors, Country (Year) | Number of Transplant Biopsies (Transplant + Native Biopsies) | Number of Transplant Biopsies With DDAVP Used (%) | Criteria for Use of DDAVP | Dose of DDAVP | Effects of DDAVP on Outcomes and Adverse Events |
|-------------------------|---------------------------------------------------------------|---------------------------------------------------|---------------------------|--------------|---------------------------------------------|
| Reschen et al, UK (2018)\(^\text{15}^\) | 107 | 23 (21.5) | Cr >250 µmol/L | 0.4 µg/kg (max dose 28 µg) | - No comparative analysis - 1 DDAVP patient developed gross haematuria - Adverse events: NR |
| Ferguson et al, Croatia (2018)\(^\text{15}^\) | 592 (725) | NR (82 in total cohort) | eGFR <30 – 45 mL/min/1.73 m\(^2\) | 0.4 µg/kg | NR |
| Whittier et al, USA (2018)\(^\text{15}^\) | 938 (1705) | NR | “At discretion of attending nephrologist” | NR | NR |
| Feldmann et al, Germany (2017)\(^\text{15}^\) | 181 (500) | NR (5 in total cohort) | “Pathological findings in specific tests” | NR | NR |
| Tsai SF et al, Taiwan, ROC (2016)\(^\text{15}^\) | 269 | 269 (100) | All patients | 4 units, 30 minutes before biopsy | - No control (non-DDAVP) group - No thrombosis or hyponatraemia |
| Morgan TA et al, USA (2016)\(^\text{15}^\) | 235 (total cohort 2514) | 9 (3.8) | “Given prophylactically to treat platelet dysfunction” | NR | - More DDAVP use in group with complications (8.5% vs 2.7%, \( P = 0.08 \)) - Adverse events: NR |

**Cr**: Creatinine; **DDAVP**: Desmopressin acetate; **eGFR**: Estimated glomerular filtration rate; **NR**: Not reported; **ROC**: Republic of China; **UK**: United Kingdom; **USA**: United States of America

\(^\text{1}^\)Reschen ME, Mazzella A, Sharples E. A retrospective analysis of the utility and safety of kidney transplant biopsies by nephrology trainees and consultants. Ann Med Surg (Lond) 2018;28:6–10.

\(^\text{2}^\)Ferguson C, Winters S, Jackson S, McToal M, Low G. A retrospective analysis of complication and adequacy rates of ultrasound-guided native and transplant non-focal renal biopsies. Abdom Radiol (NY) 2018;43:2183–9.

\(^\text{3}^\)Whittier WL, Gashiti C, Saltzberg S, Korbet S. Comparison of native and transplant kidney biopsies: diagnostic yield and complications. Clin Kidney J 2018;11:616–22.

\(^\text{4}^\)Feldmann Y, Böer K, Wolf G, Busch M. Complications and monitoring of percutaneous renal biopsy – a retrospective study. Clin Nephrol 2018;89:260–8.

\(^\text{5}^\)Tsai SF, Chen CH, Shu KH, Cheng CH, Yu TM, Chuang YW, et al. Current safety of renal allograft biopsy with indication in adult recipients: an observational study. Med 2016;95:e2816.

\(^\text{6}^\)Morgan TA, Chandran S, Burger IM, Zhang CA, Goldstein RB. Complications of ultrasound-guided renal transplant biopsies. Am J Transpl 2016;16:1298–305.
times and objective measurements of platelet function do not correlate with the development of bleeding complications during renal biopsies.\textsuperscript{31–33}

The risk of biopsy-associated bleeding complications may be lower in transplanted kidneys than native kidneys.\textsuperscript{12,24} Renal allograft biopsies may be less challenging technically as transplanted kidneys are located more superficially and do not move with respiration. Any bleeding that occurs may potentially be more easily controlled with direct manual compression. Renal arteriolar vasoconstriction and the reduction of renal blood flow with the use of calcineurin inhibitors\textsuperscript{35} may also possibly attenuate the risk of bleeding during renal allograft biopsies. As such, evidence from studies involving native renal biopsies may not necessarily apply to renal allograft biopsies and the risk-to-benefit ratio for DDAVP use may be different.

Our study may not have been able to demonstrate a significant difference in the bleeding risk between the 2 groups due to a higher proportion of cases with risk factors for bleeding such as renal impairment and anaemia in the DDAVP group. Moreover, due to a low event rate of 8.2\% which is consistent with other studies,\textsuperscript{2,6,10,12–14} our study was not adequately powered to detect the effect of DDAVP on bleeding and statistical adjustment of possible confounders was limited. However, a study adequately powered to detect an effect size of 50\% would have required a sample size of at least 411—assuming an event rate of 10\%, a 1-sided alpha error rate of 5\% and power of 80\%. Furthermore, our study did show a trend towards lower risk of peri-nephric haematoma in the DDAVP group, raising the possibility of a type 2 error, even though repeat imaging was not routine. However, despite adjustment for renal function and each of the risk factors of bleeding, DDAVP still did not alter the bleeding risk.

DDAVP may also not have been shown to reduce bleeding in our study because the median dose received at 0.2 μg/ kg, was lower than the 0.3–0.4 μg/kg dose typically used for prevention of uremic bleeding.\textsuperscript{18} A previous RCT suggested a dose effect when it showed that 0.4 μg/kg of DDAVP resulted in fewer blood transfusions compared with 0.2 μg/kg of DDAVP in rheumatoid arthritis patients undergoing hip arthroplasty.\textsuperscript{37}

DDAVP is not without risk. Reported adverse effects include headache, giddiness, nausea, flushing, abdominal pain, diarrhoea, hypotension, tachycardia and hyponatraemia.\textsuperscript{20,21} While previous studies involving native renal biopsies were not associated with major adverse events,\textsuperscript{15,16} severe hyponatraemia with neurological complications have been reported following the administration of DDAVP prior to renal allograft biopsies.\textsuperscript{17} Fluid restriction 1 hour prior to and 9 hours after the administration of DDAVP has been recommended to prevent hyponatraemia.\textsuperscript{17}

In addition to conditions that may also affect the non-transplant population (such as cardiac failure and liver cirrhosis), renal transplant recipients may be exposed to other factors and medications that predispose them to hyponatraemia.\textsuperscript{18} Early post-transplant hyponatraemia may result from the use of hypotonic solutions and tubular sodium loss from hypoxic-ischaemic allograft injury.\textsuperscript{38} Renal impairment, along with tubular dysfunction, from allograft rejection or drug-induced interstitial nephritis (e.g. cotrimoxazole)\textsuperscript{40} may affect urinary sodium absorption and free water excretion. Cyclosporine has been reported to reduce proximal sodium tubular reabsorption while tacrolimus may cause salt-losing nephropathy by inducing aldosterone resistance.\textsuperscript{41–44} High-dose corticosteroids or calcineurin inhibitors may lead to drug-induced hyperglycaemia\textsuperscript{45} and hypertonic hyponatraemia. IVIG is known to cause both pseudo-hyponatraemia and “true” hypo-osmolar hyponatraemia.\textsuperscript{46,47} Therefore, renal transplant recipients may be at higher risk of developing hyponatraemia following administration of DDAVP than the non-transplant population.

Fluid intake of <1 L was associated with lower incidence of hyponatraemia and no cases of severe hyponatraemia, suggesting fluid restriction may be protective of DDAVP-associated hyponatraemia. Recommendation for fluid restriction of <1 L over 24 hours, after DDAVP administration for renal biopsy should be considered, if possible. Lower baseline serum sodium levels and recent IVIG use were also associated with development of hyponatraemia suggesting DDAVP should be used with caution in patients with these risk factors.

Several cases of acute myocardial infarction following a single dose of DDAVP have also been reported.\textsuperscript{19} A previous systematic review on the use of DDAVP to decrease perioperative blood loss during cardiac surgeries also showed an increased risk of myocardial infarctions,\textsuperscript{19} though this association was not found in more recent meta-analyses.\textsuperscript{48,49} Given that ischaemic heart disease is common in renal transplant recipients, DDAVP should be used with caution\textsuperscript{50} although there were no thrombotic events in our study.

Given its single-centre, retrospective nature, our study is prone to bias and confounding and its generalisability is limited. Our study consisted mainly of patients of Asian descent and its results may not apply to other ethnicities. DDAVP use and fluid management were not standardised and repeat investigations including imaging, serum and urine osmolality were not routine. However, to our knowledge, this is the first study investigating the efficacy and safety of DDAVP for the prevention of bleeding complications
during renal allograft biopsies. Our study also has one of the largest samples of prebiopsy DDAVP use in renal transplant recipients. Moreover, the results persisted after adjustment for possible confounders within the limitations of our dataset.

Conclusion

The effect of using intravenous DDAVP to reduce bleeding risk during renal allograft biopsy is unclear and may increase the risk of hyponatraemia. If DDAVP is used, we suggest that patients be fluid-restricted and monitored for complications such as hyponatraemia. We call for an adequately powered prospective RCT in the renal transplant population to clarify these outcomes.

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| Variable | Bleeding (n = 16) | Non-Bleeding (n = 179) | Odds Ratio | 95% Confidence Interval | P Value |
|----------|------------------|------------------------|------------|-------------------------|---------|
| Age, year (IQR) | 51.6 (15.3) | 50.5 (13.5) | 1.00 | 0.96 - 1.05 | 0.98 |
| Males (vs females), n (%) | 10 (62.5) | 99 (55.3) | 1.35 | 0.48 - 4.11 | 0.58 |
| Ethnicity, n (%) | Chinese 10 (62.5) | Malay 2 (12.5) | 0.60 | 0.09 - 3.38 | 0.51 |
| | Indian 2 (12.5) | Others 2 (12.5) | 1.70 | 0.25 - 7.33 | 0.52 |
| Cause of ESRD, n (%) | Glomerulonephritis 9 (56.3) | Hypertension 2 (12.5) | 2.59 | 0.36 - 11.72 | 0.26 |
| | Diabetes mellitus 5 (31.3) | Others 0 (0) | 10.16 | 2.58 - 38.96 | 0.001 |
| | DDRT (versus LDRT), n (%) | 10 (62.5) | 6 (3.4) | 3.97 | 0.53 - 20.05 | 0.12 |
| | Years since transplant, years (IQR) | 0.6 (8.7) | 4.2 (9.5) | 0.95 | 0.86 - 1.03 | 0.14 |
| Maintenance immunosuppression, n (%) | Prednisolone 15 (93.8) | Tacrolimus 8 (50) | 1.03 | 0.37 - 2.88 | 0.95 |
| | Cyclosporin A 7 (43.8) | Mycophenolate 15 (93.8) | 4.32 | 0.55 - 33.68 | 0.16 |
| | Azathioprine 0 (0) | Everolimus 1 (6.3) | 0.85 | 0.10 - 6.96 | 0.88 |
| | Sirolimus 0 (0) | aPTT: Activated partial thromboplastin time; BP: Blood pressure; DDAVP: Desmopressin acetate; DDRT: Deceased donor renal transplant; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; IQR: Interquartile range; IVIG: Intravenous immunoglobulin; LDRT: Living donor renal transplant; NA: Not applicable; PT: Prothrombin time |
## Supplementary Table 1. Univariable Modelling for Overall Bleeding Complications (Cont’d)

| Variable                              | Bleeding (n = 16) | Non-Bleeding (n = 179) | Odds Ratio | 95% Confidence Interval | P Value |
|---------------------------------------|-------------------|------------------------|------------|--------------------------|---------|
| Comorbidities, n (%)                  |                   |                        |            |                          |         |
| Hypertension                          | 15 (93.8)         | 133 (74.3)             | 5.19       | 1.01 ‒ 95.1              | 0.12    |
| Diabetes mellitus                     | 6 (37.5)          | 41 (22.9)              | 2.02       | 0.65 ‒ 5.78              | 0.20    |
| Ischaemic heart disease               | 0 (0)             | 16 (8.9)               | NA         | NA                       | NA      |
| Hypothyroidism                        | 0 (0)             | 8 (4.5)                | NA         | NA                       | NA      |
| Congestive cardiac failure            | 0 (0)             | 0 (0)                  | NA         | NA                       | NA      |
| Liver cirrhosis                       | 0 (0)             | 0 (0)                  | NA         | NA                       | NA      |
| Clinical parameters                   |                   |                        |            |                          |         |
| Weight, kg (IQR)                      | 65 (19.7)         | 67.7 (21.1)            | 0.99       | 0.96 ‒ 1.02              | 0.56    |
| Body mass index (IQR)                 | 23.1 (4.2)        | 25.4 (6.2)             | 0.97       | 0.88 ‒ 1.07              | 0.60    |
| Systolic BP, mmHg (IQR)               | 140 (13.0)        | 130 (20.0)             | 1.02       | 0.99 ‒ 1.04              | 0.26    |
| Diastolic BP, mmHg (IQR)              | 75 (15.2)         | 77 (10.0)              | 1.01       | 0.96 ‒ 1.06              | 0.69    |
| Prebiopsy laboratory                  |                   |                        |            |                          |         |
| Haemoglobin, g/dL (IQR)               | 9.6 (2.7)         | 10.5 (2.3)             | 0.73       | 0.53 ‒ 0.98              | 0.04    |
| Platelets, × 10^9/L (IQR)             | 189 (68.7)        | 236 (117.5)            | 0.99       | 0.98 ‒ 1.00              | 0.002   |
| PT, seconds (IQR)                     | 10.6 (1.0)        | 10.3 (0.7)             | 1.94       | 0.87 ‒ 4.26              | 0.11    |
| aPTT, seconds (IQR)                   | 27.3 (4.0)        | 26.7 (2.9)             | 1.17       | 0.94 ‒ 1.45              | 0.16    |
| Urea, mmol/L (IQR)                    | 13.2 (6.5)        | 13.3 (6.1)             | 0.99       | 0.88 ‒ 1.09              | 0.80    |
| Creatinine, µmol/L (IQR)              | 294 (256.7)       | 229 (126.5)            | 1.00       | 1.00 ‒ 1.01              | 0.13    |
| eGFR, mL/min/1.73 m² (IQR)            | 18.4 (19.6)       | 23.7 (15.1)            | 0.98       | 0.93 ‒ 1.03              | 0.43    |
| Urine protein-to-creatinine ratio, g/g (IQR) | 0.5 (2.8)       | 1 (3.1)                | 1.01       | 0.84 ‒ 1.15              | 0.85    |
| Nephrotic range proteinuria, n (%)    | 4 (30.8)          | 56 (33.3)              | 0.89       | 0.26 ‒ 3.01              | 0.85    |
| Medication use                        |                   |                        |            |                          |         |
| Antiplatelet, n (%)                   | 0 (0)             | 1 (0.6)                | NA         | NA                       | NA      |
| Anticoagulation, n (%)                | 0 (0)             | 0 (0)                  | NA         | NA                       | NA      |
| Fresh frozen plasma, n (%)            | 1 (6.3)           | 1 (0.6)                | 11.87      | 0.45 ‒ 310.42            | 0.09    |
| Vitamin K, n (%)                      | 0 (0)             | 1 (0.6)                | NA         | NA                       | NA      |
| Antihypertensive, n (%)               | 13 (81.3)         | 151 (84.4)             | 0.8        | 0.24 ‒ 3.67              | 0.75    |
| DDAVP, n (%)                          | 8 (50.0)          | 90 (50.3)              | 0.99       | 0.35 ‒ 2.8               | 0.98    |
| Dose of DDAVP, mg (IQR)               | 16 (4.0)          | 12 (4.0)               | 1.12       | 0.88 ‒ 1.39              | 0.34    |
| Dose of DDAVP per body weight, mg/kg (IQR) | 0.2 (0)        | 0.2 (0)                | 24.34      | 0 – 55107336.18          | 0.68    |

aPTT: Activated partial thromboplastin time; BP: Blood pressure; DDAVP: Desmopressin acetate; DDRT: Deceased donor renal transplant; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; IQR: Interquartile range; IVIG: Intravenous immunoglobulin; LDRT: Living donor renal transplant; NA: Not applicable; PT: Prothrombin time
Supplementary Table 2. Multivariable Modelling for Overall Bleeding Complications With Desmopressin Acetate Use as Co-Variate

| Variable                        | Adjusted Odds Ratio | 95% Confidence Interval | *P* Value |
|--------------------------------|---------------------|-------------------------|-----------|
| DDAVP adjusted by eGFR         | 0.79                | 0.26 – 2.43             | 0.68      |
| eGFR, mL/min/1.73 m²            | 0.98                | 0.93 – 1.03             | 0.37      |
| DDAVP adjusted by urea         | 1.06                | 0.34 – 3.27             | 0.93      |
| Urea, mmol/L                   | 0.98                | 0.88 – 1.10             | 0.79      |
| DDAVP adjusted by creatinine   | 0.69                | 0.23 – 2.12             | 0.52      |
| Creatinine, µmol/L             | 1.003               | 1.00 – 1.01             | 0.08      |
| DDAVP adjusted by diuretic use | 0.93                | 0.32 – 2.67             | 0.89      |
| Diuretic use                   | 1.31                | 0.44 – 3.93             | 0.63      |
| DDAVP adjusted by DM as cause of ESRD | 1.24       | 0.41 – 3.70             | 0.70      |
| DM as cause of ESRD (vs others) | 11.65               | 3.10 – 43.75            | <0.001    |
| DDAVP adjusted by haemoglobin  | 0.84                | 0.30 – 2.39             | 0.75      |
| Haemoglobin, g/dL              | 0.72                | 0.53 – 0.99             | 0.04      |
| DDAVP adjusted by platelet     | 1.10                | 0.38 – 3.16             | 0.86      |
| Platelet, × 10⁹/L              | 0.99                | 0.979 – 0.996           | 0.006     |
| DDAVP adjusted by FFP          | 0.88                | 0.30 – 2.52             | 0.80      |
| FFP                            | 12.71               | 0.72 – 225.73           | 0.08      |
| DDAVP adjusted by prednisolone | 0.99                | 0.35 – 2.79             | 0.98      |
| Prednisolone                   | 0.084               | 0.005 – 1.42            | 0.08      |

DDAVP: Desmopressin acetate; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; FFP: Fresh frozen plasma
Supplementary Table 3. Univariable Modelling for Hyponatraemia

| Variable                        | Hyponatraemia (n = 70) | Non-Hyponatraemia (n = 107) | Odds Ratio | 95% Confidence Interval | P Value |
|--------------------------------|------------------------|-----------------------------|------------|-------------------------|---------|
| Age, year (IQR)                | 50.1 (12.7)            | 50.5 (16.2)                 | 0.99       | 0.97 – 1.02             | 0.62    |
| Males (vs females), n (%)      | 40 (57.1)              | 60 (56.1)                   | 1.04       | 0.57 – 1.92             | 0.89    |
| Ethnicity, n (%)               |                        |                             |            |                         |         |
| Chinese                        | 44 (62.9)              | 73 (68.2)                   | -          | -                       | -       |
| Malay                          | 18 (25.7)              | 20 (18.7)                   | 1.49       | 0.71 – 3.13             | 0.29    |
| Indian                         | 4 (5.7)                | 10 (9.3)                    | 0.66       | 0.20 – 2.24             | 0.51    |
| Others                         | 4 (5.7)                | 4 (3.7)                     | 1.66       | 0.40 – 6.97             | 0.49    |
| Cause of ESRD, n (%)           |                        |                             |            |                         |         |
| Glomerulonephritis             | 47 (67.1)              | 77 (72.0)                   | -          | -                       | -       |
| Hypertension                   | 4 (5.7)                | 7 (6.5)                     | 0.94       | 0.26 – 3.37             | 0.92    |
| Diabetes mellitus              | 4 (5.7)                | 7 (6.5)                     | 0.94       | 0.26 – 3.37             | 0.92    |
| Others                         | 15 (21.4)              | 16 (15.0)                   | 1.54       | 0.70 – 3.39             | 0.29    |
| DDRT (vs LDRT), n (%)          | 36 (51.4)              | 72 (67.9)                   | 0.50       | 0.27 – 0.93             | 0.03    |
| Years since transplant, years (IQR) | 3.6 (9.3)     | 3.9 (8.9)                   | 0.96       | 0.95 – 1.04             | 0.81    |
| Maintenance immunosuppression, n (%) |            |                             |            |                         |         |
| Prednisolone                   | 70 (100)               | 105 (98.1)                  | NA         | NA                      | NA      |
| Tacrolimus                     | 40 (57.1)              | 52 (48.6)                   | 1.41       | 0.77 – 2.59             | 0.27    |
| Cyclosporin A                  | 23 (32.9)              | 46 (43.0)                   | 0.65       | 0.35 – 1.22             | 0.18    |
| Mycophenolate                  | 52 (74.3)              | 90 (84.1)                   | 0.55       | 0.26 – 1.15             | 0.11    |
| Azathioprine                   | 3 (4.3)                | 7 (6.5)                     | 0.64       | 0.16 – 2.56             | 0.53    |
| Everolimus                     | 7 (10.0)               | 7 (6.5)                     | 1.59       | 0.53 – 4.74             | 0.41    |
| Sirolimus                      | 2 (2.9)                | 2 (1.9)                     | 1.54       | 0.21 – 11.2             | 0.67    |
| Comorbidities, n (%)           |                        |                             |            |                         |         |
| Hypertension                   | 49 (70.0)              | 82 (76.6)                   | 0.71       | 0.36 – 1.40             | 0.33    |
| Diabetes mellitus              | 20 (28.6)              | 22 (20.6)                   | 1.55       | 0.77 – 3.11             | 0.22    |
| Ischaemic heart disease        | 6 (8.6)                | 7 (6.5)                     | 1.34       | 0.43 – 4.17             | 0.61    |
| Hypothyroidism                 | 5 (7.1)                | 3 (2.8)                     | 2.67       | 0.62 – 11.5             | 0.19    |
| Congestive cardiac failure     | 0 (0)                  | 0 (0)                       | NA         | NA                      | NA      |
| Liver cirrhosis                | 0 (0)                  | 0 (0)                       | NA         | NA                      | NA      |
| Clinical parameters            |                        |                             |            |                         |         |
| Weight, kg (IQR)               | 69.1 (21.6)            | 66.5 (23.1)                 | 1.002      | 0.98 – 1.02             | 0.87    |
| Body mass index (IQR)          | 24.9 (8.0)             | 25.3 (5.6)                  | 1.00       | 0.94 – 1.06             | 0.99    |
| Systolic BP, mmHg (IQR)        | 128 (20)               | 130 (20)                    | 1.00       | 0.98 – 1.01             | 0.63    |
| Diastolic BP, mmHg (IQR)       | 79 (19)                | 75 (10)                     | 0.99       | 0.96 – 1.02             | 0.51    |
| Prebiopsy laboratory           |                        |                             |            |                         |         |
| Haemoglobin, g/dL (IQR)        | 10.2 (2.6)             | 10.4 (2.6)                  | 0.88       | 0.74 – 1.04             | 0.14    |
| Platelets, × 10⁹/L (IQR)       | 234 (90)               | 229 (116)                   | 1.00       | 0.996 – 1.003           | 0.90    |
| Urea, mmol/L (IQR)             | 13.9 (6.7)             | 13.2 (6.4)                  | 1.02       | 0.96 – 1.08             | 0.53    |
| Creatinine, µmol/L (IQR)       | 261 (160)              | 233 (184)                   | 1.00       | 0.998 – 1.003           | 0.47    |
| eGFR, mL/min/1.73 m² (IQR)     | 21.1 (15.8)            | 23.5 (15.5)                 | 0.99       | 0.96 – 1.02             | 0.42    |
| Urine protein-to-creatinine ratio, g/g (IQR) | 1.46 (3.85) | 0.91 (2.75) | 1.01 | 0.91 – 1.11            | 0.92    |
| Nephrotic range proteinuria, n (%) | 23 (36.5)        | 32 (31.4)                   | 1.26       | 0.65 – 2.44             | 0.50    |
| Sodium, mmol/L (IQR)           | 137 (2)                | 139 (4)                     | 0.75       | 0.66 – 0.85             | <0.001  |

BP: Blood pressure; DDAVP: Desmopressin acetate; DDRT: Deceased donor renal transplant; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; IQR: Interquartile range; LDRT: Living donor renal transplant; NA: Not applicable
### Supplementary Table 3. Univariable Modelling for Hyponatraemia (Cont’d)

| Variable | Hyponatraemia (n = 70) | Non-Hyponatraemia (n = 107) | Odds Ratio | 95% Confidence Interval | P Value |
|----------|------------------------|-----------------------------|------------|-------------------------|---------|
| Medication use | | | | | |
| Antihypertensive, n (%) | 54 (77.1) | 92 (86.0) | 0.55 | 0.25 – 1.20 | 0.13 |
| Diuretic, n (%) | 17 (24.3) | 40 (37.4) | 0.54 | 0.27 – 1.05 | 0.07 |
| Loop diuretic, n (%) | 17 (24.3) | 38 (35.5) | 0.58 | 0.30 – 1.14 | 0.12 |
| Thiazide diuretic, n (%) | 1 (1.4) | 2 (1.9) | 0.77 | 0.07 – 8.68 | 0.83 |
| Potassium-sparing diuretic, n (%) | 4 (5.7) | 2 (1.9) | 3.18 | 0.57 – 17.86 | 0.19 |
| Intravenous immunoglobulin, n (%) | 7 (10.0) | 3 (2.8) | 3.85 | 0.96 – 15.44 | 0.06 |
| Opioid, n (%) | 11 (15.7) | 15 (14.0) | 1.14 | 0.49 – 2.66 | 0.76 |
| Bactrim, n (%) | 5 (7.1) | 9 (8.4) | 0.84 | 0.27 – 2.61 | 0.76 |
| Proton pump inhibitors, n (%) | 7 (10.0) | 9 (8.4) | 1.21 | 0.43 – 3.41 | 0.72 |
| Ciprofloxacin, n (%) | 3 (4.3) | 3 (2.8) | 1.55 | 0.30 – 7.92 | 0.60 |
| New sodium-lowering medications 2 weeks prior, n (%) | 18 (25.7) | 22 (20.6) | 1.34 | 0.66 – 2.73 | 0.42 |
| Fluid intake on biopsy day, per 100 mL (IQR) | 16.8 (11.2) | 11.0 (10.8) | 1.04 | 1.004 – 1.08 | 0.03 |
| DDAVP, n (%) | 43 (61.4) | 49 (45.8) | 1.89 | 1.02 – 3.48 | 0.04 |
| Dose of DDAVP, mg (IQR) | 13.0 (4.0) | 12.0 (4.0) | 1.10 | 0.96 – 1.27 | 0.18 |
| Dose of DDAVP per body weight, mg/kg (IQR) | 0.20 (0.06) | 0.21 (0.06) | 0.19 | 0.00 – 2005.71 | 0.72 |

BP: Blood pressure; DDAVP: Desmopressin acetate; DDRT: Deceased donor renal transplant; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; IQR: Interquartile range; LDRT: Living donor renal transplant; NA: Not applicable

### Supplementary Table 4. Multivariable Modelling for Hyponatraemia

| Variable | Adjusted Odds Ratio | 95% Confidence Interval | P Value |
|----------|---------------------|-------------------------|---------|
| Desmopressin acetate, n (%) | 3.20 | 1.35 – 7.57 | 0.008 |
| eGFR, mL/min/1.73 m² (IQR) | 0.97 | 0.93 – 1.01 | 0.11 |
| Prebiopsy sodium, mmol/L (IQR) | 0.73 | 0.63 – 0.85 | <0.001 |
| Diuretic, n (%) | 0.46 | 0.20 – 1.05 | 0.07 |
| Intravenous immunoglobulin, n (%) | 5.34 | 1.01 – 28.21 | 0.05 |
| Fluid intake on biopsy day, per 100 mL (IQR) | 1.06 | 1.01 – 1.11 | 0.01 |
| DDRT (vs LDRT), n (%) | 0.55 | 0.25 – 1.18 | 0.12 |

DDRT: Deceased donor renal transplant; eGFR: Estimated glomerular filtration rate; IQR: Interquartile range; LDRT: Living donor renal transplant