Original Article

Risk factors for hyponatremia associated with desmopressin use

Jae Heon Kim[1#^], Hee Jo Yang[2#^], Sang Yeong Kim[3^], Yun Seob Song[1^]

[1]Department of Urology, Soonchunhyang University Seoul Hospital, Seoul, Republic of Korea; [2]Department of Urology, Soonchunhyang University Cheonan Hospital, Cheonan, Republic of Korea; [3]Department of Data Innovation, Soonchunhyang University Seoul Hospital, Seoul, Republic of Korea

Contributions: (I) Conception and design: JH Kim, YS Song; (II) Administrative support: SY Kim, HJ Yang; (III) Provision of study materials or patients: JH Kim, SY Kim; (IV) Collection and assembly of data: HJ Yang, YS Song; (V) Data analysis and interpretation: JH Kim, YS Song; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]Theses authors contributed equally to this work.

Correspondence to: Yun Seob Song, MD, PhD. Department of Urology, Soonchunhyang University Seoul Hospital, 59, Daesagwan-ro, Yongsan-gu, Seoul 04401, Republic of Korea. Email: schurology1@gmail.com.

Background: Nocturia is a urinary symptom that can significantly impact a patient's quality of life. Desmopressin is prescribed for adults with nocturia. However, desmopressin use is associated with hyponatremia. The objective of this study was to assess the rate of hyponatremia in patients prescribed desmopressin and associated risk factors.

Methods: Study subjects were patients who were newly prescribed desmopressin 0.1 mg (tablet) between January 1, 2015 (the start of available data) and December 1, 2020. Factors such as patients' baseline characteristics, comorbidities, and concomitant medications were analyzed to compare risk factors for hyponatremia (≤135 mmol/dL).

Results: A total of 918 adults were included in this study. The rate of hyponatremia was 4.4 % in patients with desmopressin. The hyponatremia group was older than non-hyponatremia group (71.0 *vs.* 61.6 years, P<0.001). The hyponatremia group had a higher prevalence of hypertension as a comorbidity. Although hypertension was more common in males than in females, the difference was not statistically significant (4.6% in male *vs.* 3.5% in female, P=0.65). Patients with hyponatremia were more likely to be taking angiotensin receptor blockers or thiazides than those without hyponatremia.

Conclusions: Hyponatremia occurred in 4.4% of patients with desmopressin. Risk factors of hyponatremia were age, comorbidities, concurrent medication and decreased estimated glomerular filtration rate (eGFR) level. Thus, care should be taken when administering desmopressin to these patients.

Keywords: Desmopressin; complication; hyponatremia

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Introduction

Nocturia is defined as waking to pass urine during the main sleep period based on the International Continence Society (ICS) (1). Nocturia is often multifactorial in etiology. It might be due to sleep disorder, impaired bladder storage (including bladder overactivity or reduced bladder capacity), urinary factors (including global or nocturnal polyuria), and others, including medication or fluid intake (2,3). Nocturia, like other urinary symptoms, increases with advancing age of patients. Sleep deprivation due to nocturia can lead to

^ ORCID: Jae Heon Kim, 0000-0002-4490-3610; Hee Jo Yang, 0000-0002-7195-806X; Sang Yeong Kim, 0000-0002-3630-0086; Yun Seob Song, 0000-0002-0909-3341.

daytime fatigue, lower self-esteem, and worsening mental health. In particular, nocturia in the elderly is associated with an increased risk of nighttime falls and subsequent fractures (4,5).

Desmopressin acetate, a synthetic analog of 8-arginine vasopressin, can act within collecting ducts to increase water reabsorption in kidneys and reduce urine production (6,7). Desmopressin is prescribed for patients with nocturia as it can reduce the number of nocturnal voids (7-11).

The efficacy and safety of desmopressin in patients with nocturia have been demonstrated in several randomized controlled trials (12-14). As a result, several guidelines recommend the use of desmopressin in men under 65 years of age with nocturia caused by nocturnal polyuria (15). However, a meta-analysis has identified that desmopressin use is associated with a 5.1-fold higher odds of hyponatremia compared to placebo. Approximately 5% of patients prescribed desmopressin experiencing hyponatremia (7). The risk of hyponatremia increases after desmopressin use in the elderly. Thus, it is especially important to be cautious when using it in the elderly (16).

The primary objective of this study was to assess the rate of hyponatremia in real clinical setting for patients prescribed desmopressin. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-4/rc).

Highlight box

Key findings

- In the real world, the incidence of hyponatremia after administering 0.1 mg of desmopressin was 4.4%.
- Caution is required when using desmopressin in patients who are elderly, have impaired renal function, or are taking angiotensin receptor blockers.

What is known and what is new?

- After using desmopressin, hyponatremia occurred more in women than in men. However, there was no statistically significant difference.
- Old age is key risk factors for developing hyponatremia after using desmopressin.
- Comorbidities, concurrent medication and decreased estimated glomerular filtration rate level also could be a risk factor.

What is the implication, and what should change now?

- Caution is required when using desmopressin in patients with these risk factors.

Methods

Study population and design

Patients who were newly prescribed desmopressin in Soonchunhyang University Seoul Hospital between January 1, 2015 (the start of available data) and December 1, 2020 were retrospectively analyzed. Complete voiding function evaluations, including urinalysis, serum electrolytes, and blood tests such as prostate-specific antigen in case of male, uroflowmetry, post-void residual volume measurement, symptom questionnaires (International Prostate Symptom Score), and voiding diary, were performed for patients who visited for voiding difficulty. Nocturia was defined as waking up at least once a night to void, according to the ICS definition. Desmopressin was administered in the form of 0.1 mg tablets before bedtime for nocturnal polyuria. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was exempted from ethical approval and individual consent was waived by the Institutional Review Board of the Soonchunhyang University Seoul Hospital due to its retrospective nature.

The initiation date of the desmopressin prescription was employed as the entry date. Desmopressin new users were characterized as patients who had not been prescribed either medication in the 180 days leading up to the index (17,18). Patients with any of the following diseases in the 180 days prior to entry were excluded: a diagnosis of malignancy, hyponatremia, diabetes insipidus, hemophilia A, Von Willebrand disease, or end-stage renal disease requiring dialysis. Serum sodium was measured before treatment, at 3 to 7 days after initiation, and as necessary during treatment, particularly when hyponatremia was suspected. Hyponatremia was defined as serum sodium levels below 135 mmol/dL. Medication administration was discontinued when hyponatremia was found. In cases where desmopressin was deemed necessary for a patient with congestive heart failure, a consultation was conducted with the cardiology department, and desmopressin was administered with the agreement of the cardiologist.

Study outcomes

The primary outcome was the incidence of hyponatremia at 3 months after being prescribed desmopressin. Risk factors for rate of hyponatremia were evaluated at the secondary outcome. We collected data of baseline characteristics, chronic medical conditions (for example, hypertension, coronary artery

disease, stroke), and concomitant medications (for example, antihypertensives, antipsychotics) for each patient.

Statistical analysis

The probability of being prescribed desmopressin was calculated using a multivariable logistic regression model. The *t*-test, and chi-square test were used to compare means. P<0.05 was considered to be statistically significant. Receiver operating characteristic (ROC) analysis was used to clarify cutoff points of predictive factors for incidence of hyponatremia. All analyses were performed using Aetion platform version 3.11 and R version 3.5.0.

Results

Baseline profiles

We identified 918 adults who satisfied study inclusion and exclusion criteria. The median duration of follow-up was 51 days (interquartile range, 42 to 121 days). Overall, the mean age was approximately 70 years. Females accounted for 21.7%. Baseline sodium levels were similar between both groups at 141.3 and 139.4 mmol/L, retrospectively (normal range, 135–145 mmol/L) (*Table 1*).

Rate of hyponatremia

At 90 days after being prescribed desmopressin, the percentage of hyponatremia was 4.4 (40 out of 918) (*Table 1*).

Kaplan-Meier curve for the rate of hyponatremia demonstrated the rate of hyponatremia deceased abruptly at 7 days after treatment with desmopressin (*Figure 1*).

Age

In the hyponatremia group, patients were older than non-hyponatremia group. At 90 days after being prescribed desmopressin, hyponatremia occurred more prevalent in individuals over 70 years old than the overall average, with the highest incidence observed in those aged 70 to 79 years (*Table 1*). Hyponatremia was not observed in patients under age of 40 years (*Figure 2*).

Gender

Of the total patients, 719 were males and 199 were females (78.3% *vs.* 21.7%). Hyponatremia occurred in 4.6% (33 out of 719) of men and 3.5% (7 out of 192) of women, showing no statistically significant difference between groups (P=0.65) (*Table 1*).

Comorbidity

Hyponatremia was more common in patients with hypertension. Hypertension rate was 55.0% (22 out of 40) in those with hyponatremia compared with 21.5% (189 out of 878) in those without hyponatremia (P<0.001). Hyponatremia occurred in 10.4% (22 out of 211) of hypertensive patients (*Table 1*).

Concurrent medication

Rate of using angiotensin receptor blockers (ARBs) was 27.5% (11 out of 40) in those with hyponatremia compared with 14.0% (123 out of 878) in those without hyponatremia (P=0.03), Rate of using thiazides was 17.5% (7 out of 40) in those with hyponatremia compared with 4.7% (41 out of 878) in those without hyponatremia (P=0.001) (*Table 1*).

Among patients taking ARBs, hyponatremia occurred in 8.2% (11 out of 134), while in the thiazide group, hyponatremia occurred in 14.6% of patients (7 out of 48). In the case of ACE inhibitors, hyponatremia was observed in 14.3% of patients, but the sample size was too small to demonstrate statistical significance.

Laboratory findings

Serum sodium level was 139.4±2.7 mmol/L in those with hyponatremia compared with 141.3±2.0 mmol/L in those without hyponatremia. Creatinine estimated glomerular filtration rate (eGFR) level was 72.9±22.2 mL/min/1.73 m^2 in those with hyponatremia compared with 85.7±19.9 mL/min/1.73 m^2 in those without hyponatremia. Increased serum sodium level and eGFR level were associated with hyponatremia (P=0.006) (*Table 1*).

Discussion

The increased risk of hyponatremia associated with desmopressin is consistent with published meta-analyses of clinical trials raising concerns about the safety of using desmopressin (7).

Less than 6% of patients prescribed desmopressin experienced hyponatremia (7,11-13). Most hyponatremia occurred soon after starting desmopressin treatment (19).

Table 1 Baseline profiles of study subjects

Characteristics	Without hyponatremia (n=878)	With hyponatremia (n=40)	P value
Age (years)	61.6±15.9	71.0±8.9	<0.001
Age group (years)			
0–9	25 (2.8)	–	0.002
10–19	18 (2.1)	–	
20–29	4 (0.5)	–	
30–39	12 (1.4)	–	
40–49	50 (5.7)	2 (5.0)	
50–59	194 (22.1)	2 (5.0)	
60–69	297 (33.8)	10 (25.0)	
70–79	220 (25.1)	21 (52.5)	
80–89	56 (6.4)	4 (10.0)	
≥90	2 (0.2)	1 (2.5)	
Days for prescription	90	29.6	
Gender			0.65
Male	686 (78.1)	33 (82.5)	
Female	192 (21.9)	7 (17.5)	
Comorbidities			
Diabetes mellitus	113 (12.9)	7 (17.5)	0.54
Hypertension	189 (21.5)	22 (55.0)	<0.001
Malignancy	122 (13.9)	8 (20.0)	0.40
Cerebrovascular accident	2 (0.2)	1 (2.5)	0.30
Dementia	12 (1.4)	–	
Congestive heart failure	2 (0.2)	–	
Concurrent medications			
ACE inhibitors	6 (0.7)	1 (2.5)	0.72
ARBs	123 (14.0)	11 (27.5)	0.03
Thiazides	41 (4.7)	7 (17.5)	0.001
SSRIs	37 (4.2)	1 (2.5)	0.90
NSAIDs	392 (44.6)	20 (50.0)	0.62
Laboratory findings			
Serum sodium (mmol/L)	141.3±2.0	139.4±2.7	0.008
Serum potassium (mmol/L)	4.2±0.4	4.3±0.5	0.77
Serum chloride (mmol/L)	103.6±2.5	102.6±4.5	0.36
Blood urea nitrogen (mg/dL)	15.8±4.4	18.3±12.1	0.38
Serum creatinine (mg/dL)	0.9±0.2	1.1±0.8	0.22
eGFR* (mL/min/1.73 m^2)	85.7±19.9	72.9±22.2	0.006

Data are presented as mean ± standard deviation or n (%). *eGFR was calculated using the chronic kidney disease epidemiology (CKD-EPI) collaboration equation. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; SSRIs, selective serotonin reuptake inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs; eGFR, estimated glomerular filtration rate.

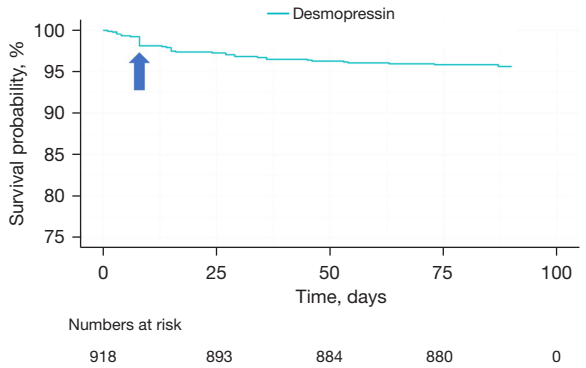

Figure 1 Kaplan-Meier curve for the rate of hyponatremia after treatment with desmopressin. Desmopressin increased the rate of hyponatremia. At 7 days after treatment with desmopressin (arrow), the rate of hyponatremia increased abruptly.

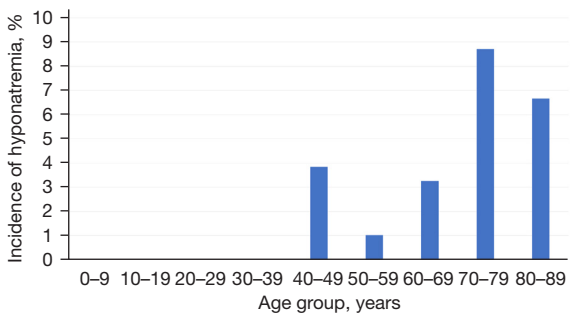

Figure 2 Frequency of hyponatremia by age group. Hyponatremia was the most common in the age group 70–79 years old of patients.

In this study, the rate of hyponatremia was 4.4% at 90 days after being prescribed desmopressin. This incidence was slightly lower than that of previous studies (*Table 1*). Kaplan-Meier curve for the rate of hyponatremia demonstrated that the rate of hyponatremia deceased abruptly at 7 days after treatment with desmopressin (*Figure 1*). This emphasizes the importance of early electrolyte monitoring after desmopressin treatment.

Old patients are more likely to receive other drug treatments, have concurrent diseases, and age-related physiological changes, all of which play important role in water and sodium balance (20). For this reason, it has been suggested that elderly patients with nocturia due to nocturnal polyuria should undergo a complete medical evaluation before using desmopressin (2). In Japan, a low-dose desmopressin is recommended for male aged 65 years and older with nocturia (21). In the present study, the rate of hyponatremia was associated with age (*Table 1*).

In previous studies, hyponatremia after desmopressin prescription was reported more frequently in females than in males (11,12). When compared with male, healthy female subjects show a more pronounced lowering of serum sodium after an intravenous dose of desmopressin (22). Moreover, the female gender has been reported to be a potential risk factor for hyponatremia during treatment with selective serotonin reuptake inhibitors and thiazide diuretics (16). In females, it is recommended to administer a lower dose of desmopressin compared to males (23). The predominance of women in other reports evidently raises the question whether gender is a risk factor. However, no predominance of women was found in this study (*Table 1*).

We identified that an increased rate of hyponatremia was associated with comorbidities. In this study, hypertension increased the rate of hyponatremia (*Table 1*). Cardiac disease has previously been identified as a risk factor for hyponatremia in patients treated with desmopressin (24). Patients were at higher risk for hyponatremia because they had more comorbid conditions (7,10).

The existence of hyponatremia in patients treated with combination medication has been reported (19,25). We identified that an increased rate of hyponatremia was associated with concurrent medication. In this study, ARBs and thiazides increased the rate of hyponatremia (*Table 1*). Renal impairment often seen in elderly patients could result in a reduced systemic clearance of desmopressin (26). In this study, serum sodium level was lower in patients with hyponatremia than in patients without hyponatremia. eGFR level was also lower in patients with hyponatremia than in patients without hyponatremia in this study.

Our study has several limitations. First, our study was a retrospective in nature. Thus, there is a potential for selection bias. As a result, investigation of other side effects besides hyponatremia was insufficient. Second, our study showed a relatively low incidence of hyponatremia compared to previous reports. This is attributed to complete medical evaluation including blood tests before administration. In addition, the number of patients with severe cardiovascular disease was small, which might have contributed to the low incidence of side effects from desmopressin. Third, this study included only results within 90 days. Some reports have shown excellent tolerability with a long-term follow-up (27). Finally, this study included only desmopressin tablets. Orally disintegrating tablets have advantages of superior long-term stability profiles compared to tablets. They are effective for chronic nocturia. They are stable with less influence from food. Additional long-term

studies would be helpful to clarify this.

Conclusions

Hyponatremia occurred in patients with desmopressin. Age, comorbidities, concurrent medication, and eGFR level were risk factors for hyponatremia. In these patients, closed follow-up will is needed if desmopressin is administered for treating nocturia due to nocturnal polyuria.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-4/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-4/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-4/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was exempted from ethical approval and individual consent was waived by the Institutional Review Board of the Soonchunhyang University Seoul Hospital due to its retrospective nature.

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