Title:

Guidance on water intake effectively improves urinary frequency in patients with nocturia

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Running title:

Water-intake guidance improves nocturia

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Abstract

Objectives: To evaluate how guidance on water intake impacts the degree of nocturia.

Methods: A total of 67 male patients were enrolled in the present study. Patients were asked to adjust their water and food intakes so that their 24-h urine production/bodyweight would be equal or lower than 30mL/kg. One month after the treatment, the therapeutic gain from and adverse effects of fluid restriction were examined by comparing the pretreatment and post-treatment value of various parameters.

Results: Overall, 65 eligible patients were evaluated. In 44 patients (67%), the frequency of nocturia was improved to one or more times. The change in frequency of nocturia showed a positive correlation with the change in nocturnal urine volume. The change in nocturnal urine volume showed a positive correlation with the changes in 24-h urine production/bodyweight, 24-h drinking volume and daytime drinking volume. The changes in 24-h urine production/body weight and daytime drinking volume were independent factors influencing therapeutic effect. None of the participants reported any adverse event.

Conclusions: In patients with a 24-h urine production/bodyweight equal or higher than 30mL/kg, guidance on water intake might be considered effective and safe as a lifestyle therapy. Water restriction should be carried out not only in the evening, but also during daytime.

Key words:

24-h urine production/bodyweight, lifestyle therapy, nocturia, nocturnal polyuria, Water intake guidance,

Introduction

Nocturia is defined as night-time urination one or more times, causing arousal from sleep.[1] It has been reported to not only reduce the quality of life (QOL) of the elderly,[2] but also have an impact on comorbidities and mortality.[3,4]

The many causes of nocturia can be classified mainly into decreased nocturnal bladder capacity and nocturnal polyuria (NP); however, it is likely that the latter accounts for many cases.[5]

NP is caused by diseases that affect vital prognosis, including cardiac, renal, and respiratory dysfunctions; a decrease in antidiuretic hormone secretion at night is also considered as a major cause of NP.[6]

Antidiuretic hormone secretion at night might be decreased not only by a primary cause, but also by increased fluid volume as a result of caffeine, alcohol, and excessive water intakes, or by lower extremity edema. Fluid intake restriction from the evening is commonly recommended.[7] This recommendation is reasonable, because it can prevent an increase in urinary output during the rest of the night. However, considering that elderly people with increased 24-h urine production (e.g. polyuria) have frequent urination and high urinary output at night,[8] and that one of the causes of increase in nocturnal urine volume (NUV) is lower extremity edema in the evening,[9] there is a high possibility that daytime water intake might contribute to NUV. However, only few previous studies have compared the association between the amount of water intake and NUV in elderly people; furthermore, regulation of water intake has not been reported thus far.

In our previous study, we reported that a 24-h urine production/bodyweight(24-h UP/BW) less

than 30 mL/kg was a contributing factor for the prevention of NP.[8] This finding suggests that in patients with 24-h UP/BW more than 30 mL/kg, decreasing the 24-h UP/BW to less than 30 mL/kg could reduce NUV and improve nocturia.

The present study aimed to evaluate the efficacy of water intake guidance in terms of the degree of nocturia improvement and the safety of the approach for use in patients with 24-h UP/BW equal or higher than 30 mL/kg.

Methods

Association between fluid intake guidance and nocturia

Between January 2005 and August 2009, 67 male patients with nocturia as a result of NP who had a 24-h UP/BW equal or higher than 30 mL/kg were enrolled in the present study. The pretreatment characteristics of the patients are shown in Table1. The study was approved by the ethical committee of Nara Medical University School of Medicine, Nara, Japan. The study participants provided verbal or written informed consent to participate in the study.

The exclusion criteria included a history of heart disease or previous treatment of heart disease, diabetes mellitus with a fasting blood glucose level of 200 mg/dL or higher, functioning adrenal tumor, renal failure (creatinine [Cr] level > 1.5 mg/dL), hydronephrosis, postvoid residual urine volume (PVR) greater than 50ml, electrolyte imbalance, frequent urinary incontinence that interferes with urinary output measurement, active urinary tract infection and diuretic use.
At the initial examination, blood pressure, blood cell count, standard chemistry panel, brain natriuretic peptide(BNP) level and urinalysis results were assessed routinely. An ultrasonographic evaluation for PVR and hydronephrosis was carried out. The participants were asked to complete

a frequency-volume chart (FVC) and record their fluid intake (time and volume). In the present study, NUV was defined as the total amount of urine voided from 22:00 to 06:00 hours, including the first voided volume after rising from bed, according to our previously reported method. [8,10] NP was defined as NUV ≥ 0.9 mL/min × sleep duration.[11] The diurnal and evening drinking volumes were defined as the total drinking volume from 06:00 to 17:00 hours, and from 17:00 to 06:00 hours, respectively.

All the patients were requested to void urine at 22:00 and 06:00 hours. A single urine sample voided at 06:00 hours was also obtained from all the patients. Details of the urinary arginine vasopressin (uAVP) measurements were described in our previous report.[10] Urine osmolarity and urinary Cr (uCr) level were determined. Plasma osmolarity was calculated using the following equation: 2 × Na (mEq/L) + blood sugar (mg/dL)/18 + blood urea nitrogen (mg/dL)/2.8.

The individual patients were asked to adjust their water and food intakes so that their 24-h UP/BW would be equal or lower than 30 mL/kg. From the record of a frequency volume chart before treatment, when the amount of 24-h drinking volume was equivalent to the amount of 24-h UP, restriction of excessive water intake was carried out. However, if there was a considerable gap between 24-h drinking volume and 24-h UP, the contents of the meal should be examined, then, we instructed patients to change meal contents. However, they were instructed to drink at least 1 L of water per day and to drink water when they experienced thirst or sweating. During the study treatment period, we allowed the patients to continue any oral maintenance therapy that they started before the initiation of the study.

One month after the treatment, the patients resumed completing their FVC and recording their

fluid intake (time and volume); blood pressure, blood cell count, uAVP, urine osmolarity, urinary sodium, and uCr level measurements, and a standard chemistry panel were also carried out. Then, we examined the therapeutic gain from and adverse effects of fluid restriction by comparing the pretreatment and post-treatment values of each parameter.

Statistical analyses

For statistical analysis, the paired *t*- test or Wilcoxon matched-pairs signed rank test was used to determine the statistical significance of the differences between the pretreatment and post-treatment parameter values. Spearman's rank correlation coefficient was used for correlation analysis. The Mann-Whitney *U* test was used for intergroup comparisons. Influencing factors were determined by carrying out a multivariate analysis using factors that were significant in the univariate analysis. A p-value of <0.05 was considered statistically significant. All the statistical analyses were carried out using the SPSS software (version 11.0 for Windows; SPSS, Chicago, IL, USA).

Results

Study participants

Of the 67 study participants, two dropped out of the study because of poor control of water intake; thus, a total of 65 patients were evaluated (median age 72 years). Of the 65 patients, 28 patients with benign prostatic hypertrophy received alpha-1 blocker before undergoing the study treatment, and 15 patients with overactive bladder received an anticholinergic agent. We classified 65 patients into two groups as follows: patients with a decrease in the frequency of nocturia by one or more times, and those without a decrease. Patients showing a decrease in the frequency of nocturia by one or more times were considered as an effective group.

Effects of the study intervention

Changes in the drinking volume, 24-h UP, NUV, and frequency of nocturia

There were significant decreases in 24-h UP, 24-h UP/BW, frequency of nocturia, NUV, 24-h drinking volume, daytime drinking volume, and evening drinking volume before and after study treatment. The mean ± SD values of the reduction in 24-h drinking volume, daytime drinking volume, and evening drinking volume were 402 ± 522, 288 ± 412, and 112 ± 277 mL, respectively. All the patients showed a decrease in the 24-h UP (612 ± 490 mL) and 24-h UP/BW (10.3 ± 7.9). The mean ± SD values of the decrease in NUV and frequency of nocturia were 300 ± 301 mL and 1.0 ± 1.2 times, respectively (Table 2). In 44 patients (67%), the frequency of nocturia was improved to one or more times (data not shown). The change in frequency of nocturia (⊿frequency of nocturia) showed a positive correlation with the change in NUV(⊿NUV; $r = 0.55$, $p < 0.0001$). ⊿NUV showed a positive correlation with the changes in 24-h UP/BW(⊿24-h UP/BW), 24-h drinking volume(⊿24-h drinking volume) and daytime drinking volume(⊿daytime drinking volume; $r = 0.62$, $p < 0.0001$; $r = 0.29$, $p = 0.02$; and $r = 0.27$, $p = 0.035$, respectively), but showed no correlation with the change in evening drinking volume (⊿evening drinking volume; $r = 0.15$, $p = 0.24$) (Fig. 1).

Side-effects of the study intervention

None of the participants reported thirst or any other adverse events. Plasma osmolarity, serum Na level and BW were compared as dehydration-related factors; no significant differences were found before and after the study treatment (Fig. 2).

Factors influencing therapeutic effect

Influencing factors were defined as the individual patient's age, BW, Cr level, BNP level, plasma osmolarity, uAVP/uCr level on waking up, urine osmolarity, 24-h UP/BW, NUV, frequency of nocturia, mean NUV, 24-h drinking volume, daytime drinking volume and evening drinking volume before undergoing the study treatment. The changes associated with the study intervention were evaluated in terms of the 24-h UP/BW(⊿24-h UP/BW), 24-h drinking volume(⊿24-h drinking volume), daytime drinking volume(⊿daytime drinking volume) and evening drinking volume(⊿ evening drinking volume) (Table 3).

In the comparison between the two groups, pretreatment plasma osmolarity, uAVP/uCr on waking up, frequency of nocturia, ⊿24-h UP/BW, ⊿24-h drinking volume and ⊿daytime drinking volume were significant factors influencing therapeutic effect in the univariate analysis. In the multivariate analysis using these factors, ⊿24-h UP/BW (odds ratio, 1.542, $p = 0.007$) and ⊿daytime drinking volume (odds ratio, 1.005, $p = 0.033$) associated with the study intervention were independent factors influencing therapeutic effect.

Discussion

In the present study, in the patients with a 24-h UP/BW equal to or higher than 30 mL/kg, the efficacy and safety of fluid restriction for use as treatment of nocturia were investigated.

Generally, drug therapy has been considered effective for nocturia, with few known adverse effects[12], and lifestyle advice, including water intake guidance, exercise therapy and routine

daytime nap, is commonly a high priority.[13] Water intake restriction is essential to reduce NUV. However, the characteristics of patients who should be indicated to receive water intake guidance have not been previously described. Nevertheless, water intake guidance is not recommended for patients with diabetes insipidus (DI) because of a risk of dehydration.[1] Generally, patients with DI and patients with polyposia differ in terms of drinking behavior. In the former patients, thirst remains; therefore, drinking behavior is influenced by thirst; in the latter patients, polyposia is mainly influenced often not by thirst, but by incorrect information from the mass media that a high water intake is good for health. Thus, drinking water to quench thirst should be encouraged when water intake guidance is provided.

Patients with a 24-h UP/BW equal to or higher than 30 mL/kg were included in the present study. For such patients, decreasing 24-h UP/BW is important to improve nocturia. Not surprisingly, water restriction might be effective in patients with a 24-h UP/BW equal to or lower than 30 mL/kg. However, Asplund et al. reported that approximately half of the patients who woke up three or more times at night for urination already underwent water restriction.[14] Therefore, water restriction was ineffective for NP in such patients. On the contrary, another study reported that water restriction was effective in patients with higher 24-h UP.[15]

In the water intake guidance intervention in the present study, the daily water intake prescribed to the patients was 2% of BW. In this guidance intervention, the patients were instructed to reduce the amount of water intake rather than to reduce the frequency of water intake because of the concern that a decrease in water intake frequency might lead to an extremely decreased amount of water intake. Soda et al. defined 2% of BW as the amount of water intake equal to the normal voided volume in healthy adults.[15] In addition, the study participants were instructed to drink

water when they experienced thirst, considering the aforementioned possible risk among patients with DI.

Through the water intake guidance intervention, the mean reduction in the frequency of nocturia was 1.0 ± 1.2 times; in 67% of the patients, the frequency of nocturia was improved to one or more times. Hashim et al. reported that water restriction by 25% was effective for nocturia, but had little clinical significance in patients with an overactive bladder.[16] Although these methods should not be compared simply on the basis of their known differences, the frequency of nocturia at baseline in the patients in the study by Hashim et al. was clearly lower by 1.4 times than that in the present study. Meanwhile, in their study, Soda et al., who carried out water intake guidance, as well as a combination therapy of sleep and exercise, reported that patients with a median frequency of 3.6 times showed a mean frequency reduction of 0.9 times and reactivity of 53.1%.[15]

Only a few reports have examined water restriction and its therapeutic effect. Soda et al. reported that the reduction of the frequency of nocturia was higher in the patients with higher 24-h UP and NUV before undergoing the study intervention, although the patients did not only receive water intake guidance.[15] In the present study, in terms of pretreatment factors, the group with positive outcomes showed higher frequency of nocturia, lower plasma osmolarity and antidiuretic hormone levels at night. The effect of water restriction was observed in the patients who received adequate hydration, although it cannot be said that only drinking volume contributed to the plasma osmolarity status. Conversely, when compared with patients with lower plasma osmolarity, the thirst sensation of patients with higher plasma osmolarity might have been so strong that water intake could not be adequately restricted.

In terms of the post-treatment factors, the group with improved frequency of nocturia had greater reduction in 24-h UP/BW, 24-h drinking volume and daytime drinking volume, suggesting that the 24-h UP and NUV was decreased by the reduced drinking volume. Furthermore, in the multivariate analysis, the improved frequency of nocturia was not influenced by the pretreatment factors, but was greatly influenced by the decreases in daytime drinking volume and 24-h UP/BW. In conventional water intake guidance, excessive water intake at night is considered to promote diuresis leading to nocturnal polyuria. Klingler et al. reported that approximately one-quarter of patients with NP drank water excessively.[5] Considering these results, the question remains as to why the decrease in daytime drinking volume contributed to the decrease in NUV in this study group. In a patient group with NP, the same drinking volume worsened lower extremity edema, resulting in a decrease in antidiuretic hormone secretion, which in turn led to an increase in NUV.[9,17]

It is inconclusive to say that daytime drinking volume mainly contributes to the fluid volume in lower extremity edema. However, considering that a certain load of water intake in patients with heart failure promotes or water retention by an antidiuretic hormone causes lower extremity edema[13], a load of daytime drinking might shift to the interstitial system and increase NUV in the present study. Not only NUV, but also night-time maximum bladder capacity and sleep duration, are known to contribute to the frequency of nocturia.[18] In the present study, sleep was prescribed to some extent; furthermore, no significant differences in night-time maximum bladder and mean bladder capacities were observed between the improved and non-improved groups, showing that only NUV influenced the frequency of nocturia.

The decrease in the 24-h UP/BW contributed to the decrease in the frequency of nocturia, which

might be naturally promoted by water restriction; however, the influence of diet cannot be denied. Furthermore, it has been reported that fruits and a diet with high water content contribute to an increase in NUV.[16]

In terms of side-effects, the intervention in the present study did not induce an increase in plasma osmolarity, and changes in Na level and BW. Considering that the reported mean UP/BW in healthy adults is 23.0 ± 1.7 mL/kg,[19] it is possible that no change was found in these parameters because of the fact that the patients in this study group received adequate hydration.

In the present study, the patients received only water intake guidance, and salt restriction was not carried out. Taking into account the possibility that daytime drinking volume might cause lower extremity edema, salt restriction and water intake guidance to prevent the daytime drinking load from shifting to the interstitial system could lead to a greater decrease in NUV and frequency of nocturia.[20]

The present study had several limitations. First, factors associated with nocturia, such as body mass index, alchol or caffeine intake, were not evaluated in this study. Second, there was no control group with which to evaluate undetectable placebo effects. Third, we defined NUV as the total amount of urine volume voided from 22:00 to 6:00 hours, according to our previously reported method. [8,10] However, sleep duration, time to go to bed and time to wake up would vary among the patients. In addition, the factors influencing the study treatment outcomes were evaluated retrospectively. Therefore, it remains unclear whether restriction of daytime drinking influences the frequency of nocturia in clinical practice, and hence, it needs to be evaluated prospectively in the future.

In patients with a 24-h UP/BW equal to or higher than 30 mL/kg, water intake guidance might be considered effective and safe as a lifestyle therapy, and should be recommended to patients before they undergo drug treatment. In the water intake guidance intervention, it is important that water restriction be carried out not only in the evening, but also during the daytime. Our present findings therefore warrant a future prospective study to establish a therapy for nocturia using more appropriate intervention procedures for NP.

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Figure legends

Fig.1

(a) Correlation between ⊿frequency of nocturia and ⊿NUV ($r=0.55, p<0.0001$). (b) Correlation between ⊿24-h UP/BW and ⊿NUV ($r=0.62, p<0.0001$). (c) Correlation between ⊿24-h drinking volume and ⊿NUV ($r=0.29, p=0.02$). (d) Correlation between ⊿daytime drinking volume and ⊿NUV ($r=0.27, p=0.035$). (e) Correlation between ⊿ evening drinking volume and ⊿NUV ($r=0.15, p=0.24$).

Fig.2

Comparison of dehydration-related factors between the pretreatment and the post-treatment groups. (a) Plasma osmolarity. (b) Serum Na level. (c) BW. The data in the bar graphs indicate mean±standard deviation.

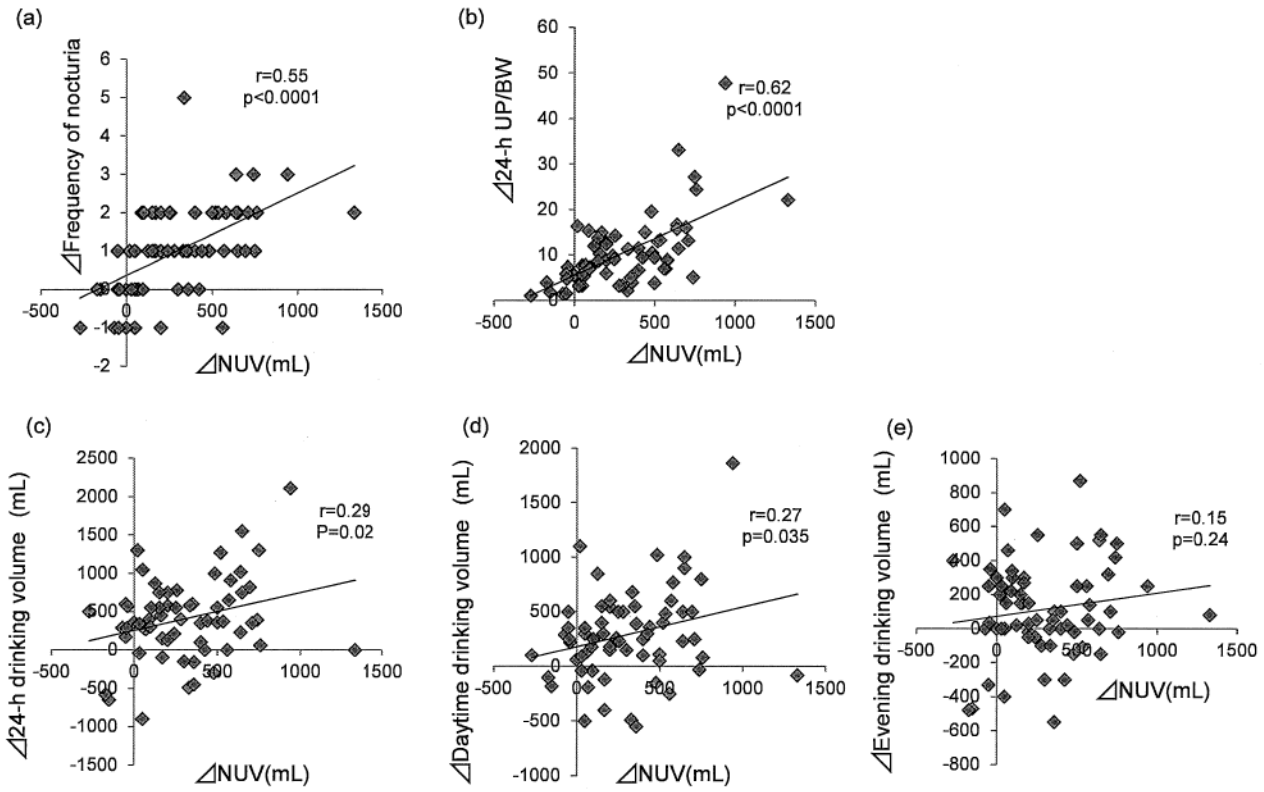
(a)
r=0.55
p<0.0001
⊿Frequency of nocturia
⊿NUV(mL)
(b)
r=0.62
p<0.0001
⊿24-h UP/BW
⊿NUV(mL)
(c)
r=0.29
P=0.02
⊿24-h drinking volume (mL)
⊿NUV(mL)
(d)
r=0.27
p=0.035
⊿Daytime drinking volume (mL)
⊿NUV(mL)
(e)
r=0.15
p=0.24
⊿Evening drinking volume (mL)
⊿NUV(mL)

Fig. 1

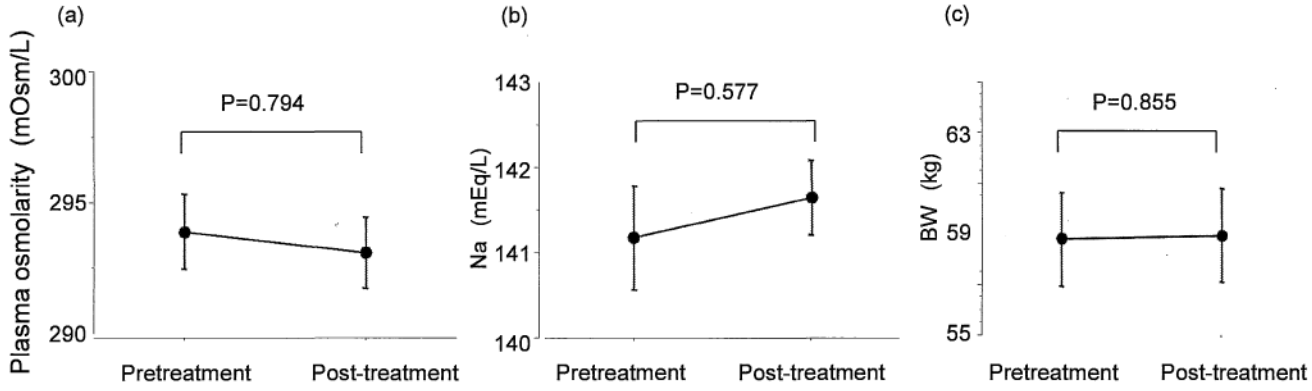
(a)
Plasma osmolarity (mOsm/L)
300
295
290
P=0.794
Pretreatment
Post-treatment
(b)
Na (mEq/L)
143
142
141
140
P=0.577
Pretreatment
Post-treatment
(c)
BW (kg)
63
59
55
P=0.855
Pretreatment
Post-treatment

Fig. 2

Table 1 Characterisitcs of patients

Mean age (years)	72 (53-91)
BW (kg)	57 (41-81)
Systolic BP (mmHg)	136 (96-164)
Diastolic BP(mmHg)	80 (45-104)
Na (mEq/L)	142 (131-145)
Ca (mg/dL)	9.3 (8.2-10.3)
Cr (mg/dL)	0.86 (0.50-1.26)
BNP (pg/mL)	33.9 (7.6-211.7)
uAVP/uCr (pg/mL/Cr)	19.7 (3.7-141.4)
Plasma osmolarity (mOsm/L)	296.45 (272.3-307.3)
Urine osmolarity (mOsm/L)	441 (243-796)
24-h UP (mL)	2070 (1290-4300)
24-h UP/BW	35.2 (30.2-70.5)
Frequency of nocturia	4 (2-11)
NUV (mL)	900 (250-1980)
NPI	0.395 (0.184-0.728)
24-h drinking volume (mL)	1600 (600-3620)
Daytime drinking volume (mL)	1020 (280-2970)
Evening drinking volume (mL)	550 (0-1790)

Score: median(range).

Table 2 Effects of study intervention

	Pretreatment	Post-treatment	Reduction value	P-value
Ca (mg/dL)	9.2±0.4	9.2±0.5	-0.0±0.4	0.727
Cr (mg/dL)	0.9±0.2	0.9±0.2	-0.0±0.1	0.618
BNP (pg/mL)	45.4±37.7	48.6±51.4	2.7±32.5	0.488
Systolic BP (mmHg)	134.8±16.3	131.0±17.2	-3.4±13.0	0.131
Diastolic BP (mmHg)	76.5±11.8	74.6±10.5	-1.7±9.7	0.164
uAVP/uCr (pg/mL/Cr)	27.9±26.4	26.8±25.6	1.2±24.4	0.618
Urine osmolarity (mOsm/L)	454.4±122.2	494.1±142.3	-39.6±139.1	0.054
24-h UP (mL)	2187±556	1575±375	612±490	<0.001
24-h UP/BW	37.1±7.4	26.8±5.2	10.3±7.9	<0.001
Frequency of nocturia	4.1±1.5	3.1±1.3	1.0±1.2	<0.001
NUV (mL)	910±321	610±242	300±301	<0.001
NPI	0.4±0.1	0.4±0.1	0.04±0.13	0.086
24-h drinking volume (mL)	1693±600	1286±524	402±522	<0.001
Daytime drinking volume (mL)	1092±441	801±350	288±412	<0.001
Evening drinking volume (mL)	600±372	488±331	112±277	0.001

Mean ±standard deviation.

Table 3 Multivariate analysis of associated variables correlating with therapeutic effect

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Age	0.967 (0.899 - 1.040)	0.363		
BW (kg)	1.004 (0.951 - 1.060)	0.893		
Cr (mg/dL)	0.510 (0.020 - 12.794)	0.682		
BNP (pg/mL)	0.989 (0.973 - 1.006)	0.197		
Plasma osmolarity (mOsm/L)	0.886 (0.787 - 0.998)	0.046	0.966 (0.806 - 1.157)	0.704
uAVP/uCr (pg/mL/Cr)	0.967 (0.944 - 0.991)	0.007	0.969 (0.935 - 1.004)	0.078
Urine osmolarity (mOsm/L)	0.999 (0.995 - 1.003)	0.683		
24-h UP/BW	1.096 (0.990 - 1.213)	0.076		
NUV (mL)	1.001 (1.000 - 1.003)	0.155		
Mean NUV (mL)	0.997 (0.989 - 1.004)	0.416		
Frequency of nocturia	2.181 (1.218 - 3.907)	0.009	2.956 (0.937 - 9.320)	0.064
24-h drinking volume (mL)	1.000 (0.999 - 1.001)	0.517		
Daytime drinking volume (mL)	1.001 (0.999 - 1.002)	0.285		
Evening drinking volume (mL)	1.000 (0.998 - 1.001)	0.816		
⊿24-h UP/BW	1.432 (1.177 - 1.742)	<0.0001	1.542 (1.128 - 2.107)	0.007
⊿24-h drinking volume (mL)	1.002 (1.001 - 1.003)	0.005	0.999 (0.995 - 1.002)	0.421
⊿ Daytime drinking volume (mL)	1.003 (1.001 - 1.005)	0.002	1.005 (1.000 - 1.010)	0.033
⊿Evening drinking volume (mL)	1.001 (0.999 - 1.003)	0.459		