

Effects of desmopressin for the treatment of nocturnal polyuria in elderly women: impact on related sleep quality

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Abstract

Introduction: We investigated the efficacy, safety, and impact of desmopressin on quality of sleep in treating nocturnal polyuria in elderly women.

Methods: We recruited 60 women over 60 years old with lower urinary tract symptoms (LUTS), including nocturia, and with nocturnal polyuria. Nocturnal polyuria was defined as nighttime urine production exceeding 33% of the 24-hour total urine volume determined by a frequency volume (FV) chart. All patients failed to respond to treatment of their underlying disease and evening fluid restriction. Desmopressin 0.1 mg was administered orally at bedtime for 12 weeks. The participants completed a series of questionnaires on the Medical Outcomes Study (MOS) sleep scale and FV chart before and after treatment.

Results: The patient population had a mean age of 69.2 ± 9.4 years (range: 61–81). The mean duration of symptoms was 61.2 ± 45.1 months. Significant decreases were evident after desmopressin treatment in the number of nocturia episodes (3.63 ± 1.61 to 2.00 ± 1.13 , $p = 0.01$), nocturnal urine volume ($p = 0.01$), nocturnal polyuria index (NPI) ($p = 0.01$), and nocturia index (NI) ($p = 0.01$). Among the categories of the MOS sleep scale, sleep index ($p = 0.003$), sleep disturbance ($p = 0.001$), snoring ($p = 0.028$), and shortness of breath ($p = 0.036$) significantly changed, with a decreased number of nocturia episodes. Adverse events were mild.

Conclusions: Desmopressin is an effective treatment for nocturnal polyuria in elderly women, where conservative treatment has failed. Sleep quality is also improved.

Introduction

Nocturia is defined as waking to void during the night; the condition is the most bothersome of the lower urinary tract symptoms (LUTS) in a significant portion of adults.^{1,2} Three main pathophysiologic categories have been suggested for

nocturia: nocturnal polyuria, low nocturnal bladder capacity, or a combination of nocturnal polyuria and low nocturnal bladder capacity. Nocturnal polyuria, an overproduction of urine at night, is considered among the primary causes of nocturia responsible for up to 70% of the nocturia cases.³

Nocturia significantly affects the elderly in terms of general health, quality of life, and especially quality of sleep.⁴ Many elderly people wake several times during the night to urinate, which causes significantly impaired quality of life, lack of sleep time, poor sleep quality, and difficulty in returning to sleep after getting up to void.⁴

Desmopressin reduces the frequency of nocturia induced by nocturnal polyuria.⁵ However, little is known about the use of desmopressin in elderly women with nocturnal polyuria. Most studies have reported on the efficacy of desmopressin for nocturia in men with any etiology, not just nocturnal polyuria.

In the present study, we evaluated the effect of desmopressin on the frequency of nocturia and nocturnal polyuria, and on the related sleep quality in elderly women. To our knowledge this is the first report assessing the use of desmopressin for nocturia induced by nocturnal polyuria in elderly women.

Methods

Participants and study design

In this prospective observational study conducted from January 2009 to December 2013, we recruited 60 women over 60 years old with lower urinary tract symptoms (LUTS), including nocturia, and with nocturnal polyuria. Nocturnal polyuria was defined as nighttime urine production exceeding 33% of the 24-hour total urine volume determined by a frequency volume (FV) chart. All patients failed to respond to treatment for their underlying disease and evening fluid restriction. Desmopressin 0.1 mg was administered orally at bedtime for 12 weeks. All patients underwent a detailed

clinical evaluation involving a complete history, physical examination, international prostatic symptom score (IPSS), urinalysis, uroflowmetric parameters including maximal flow rate (Qmax), and post-void residual (PVR). The participants completed a series of questionnaires on the Medical Outcomes Study (MOS) sleep scale and FV chart before and after treatment. All participants provided written informed consent with data collection, and the study received approval from the local ethics committee and the institutional review board. The study procedures complied with the guidelines provided by the Declaration of Helsinki.

Primary and secondary objectives

The primary objective was to assess the efficacy and safety of desmopressin treatment in patients with nocturnal polyuria. Efficacy was assessed by the number of nocturnal voiding episodes and the nocturia parameter, including nocturnal urine volume, nocturnal polyuria index (NPI), and nocturia index (NI). The secondary objective was to evaluate the effectiveness of treatment on sleep quality assessed by the MOS sleep scale. Data for these parameters were acquired at baseline and after 12 weeks of treatment.

Exclusion criteria

We excluded patients with the following factors: confused or depressed mental status, use of medications, such as sedatives or tranquilizers, use of medications that might alter or control bladder symptoms, history of previous LUTS surgery, any implication of neurogenic bladder or functional bladder outlet obstruction (BOO), symptomatic urinary tract infection, and uropathologic conditions, including urinary stones and urogenital cancer. Patients with chronic renal disease, obstructive pulmonary disease, and history of insomnia or a sleep disorder were also excluded. Patients who had received treatment with drugs known or suspected to be related with desmopressin, such as diuretics, carbamazepine, and tricyclic antidepressant, and patients with contraindications to the use of desmopressin who had a previous history of hyponatremia, diabetes insipidus, and syndrome of inappropriate antidiuretic hormone were also excluded. Patients with suspected fluid overload states, such as congestive heart failure, liver disease with hypoalbuminemia, nephrotic syndrome or lower extremity venous stasis were excluded. Finally, patients with polyuria as recorded in a voiding diary, with restricted mobility, or who worked at night were also excluded from this analysis.

FV chart

Patients were asked to complete a 3-day FV chart. They were taught by a urologist how to accurately complete a

FV chart, and were requested not to alter their usual fluid intake and voiding habits during the study. Times of morning rising going to bed at night were recorded on the FV chart. Numbers and volumes of voids were estimated by taking a mean over the 3-day study period. Nighttime was defined as the time from bedtime to rising in the morning.

MOS sleep scale

The MOS sleep measure yields a sleep problems index and a 6-scale score measuring the following: sleep disturbance (have trouble falling asleep, how long to fall asleep, sleep was not quiet, awaken during sleep time, and have trouble falling asleep again), sleep adequacy (get enough sleep to feel rested upon waking in the morning, get the amount of sleep needed), daytime somnolence (drowsy during the day, have trouble staying awake during the day, take naps), snoring, awaken with shortness of breath or with headache, and quantity of sleep.⁶ The quantity of sleep was presently scored as the average number of hours slept per night. The other scales and problems index were scored on a 0 to 100 possible range, with higher scores indicating more of the concept being measured.

Statistical analysis

SPSS (version 17 for Windows; SPSS Inc, Chicago, IL) was used for statistical analyses. Data were expressed as means \pm standard deviations and were analyzed by Student's *t* test (paired). Statistical significance was set at $p < 0.05$.

Results

The mean patient population had a mean age of 69.2 ± 9.4 years (range: 61–81 years). The mean duration of symptoms was 61.2 ± 45.1 months. The incidence of hypertension and other cardiovascular disease was 33.3% and 18.4%, respectively (Table 1). The baseline IPSS total score, storage symptoms score, voiding symptoms score, and the bother score were 20.5 ± 6.9 , 10.0 ± 2.9 , 10.4 ± 4.5 , 4.63 ± 0.80 , respectively (Table 1). The mean number of voiding episodes per night was measured (Table 1).

The overall mean change in nocturnal frequency after 12 weeks of desmopressin treatment was 1.63 times per night ($p = 0.001$). Significant increases were evident in the number of nocturia episodes compared to before treatment (3.63 ± 1.61 to 2.00 ± 1.13 , $p = 0.01$), nocturnal urine volume ($p = 0.01$), NPI ($p = 0.01$), and NI ($p = 0.01$) (Table 2). The baseline nocturnal bladder capacity index (NBCi) was 1.95 ± 1.46 ; the value more than zero indicated that decreased nocturnal bladder capacity could be a factor in some patients. However the NBCi also significantly decreased after treatment to 1.33 ± 0.67 ($p = 0.001$) (Table 2).

Table 1. Patient characteristics and comorbidities

Patients characteristics	Value
No. patients	60
Mean age (years, mean \pm SD)	69.2 \pm 9.4
Duration of symptom (months, mean \pm SD)	61.2 \pm 45.1
Additional combined disease, n (%)	
Hypertension	20 (33.3)
Diabetes mellitus	10 (16.7)
Other cardiovascular disease	11 (18.4)
Menopausal state, n (%)	38 (63.3)
Hormonal treatment, n (%)	8 (13.3)
No. nocturia episodes, n (%)	
1	2 (3.3)
2	12 (20.0)
≥ 3	46 (76.7)
IPSS (mean \pm SD)	
Total	20.5 \pm 6.9
Storage symptoms	10.0 \pm 2.9
Voiding symptoms	10.4 \pm 4.5
Quality of life	4.63 \pm 0.80
Qmax (mL/sec, mean \pm SD)	17.9 \pm 7.2
PVR (mL, mean \pm SD)	32.2 \pm 38.4

SD: standard deviation; IPSS: international prostate symptom score; Qmax: Maximal flow rate; PVR: post-void residual.

Concerning sleep quality, the subcategories of sleep index ($p = 0.003$), sleep disturbance ($p = 0.001$), snoring ($p = 0.028$), and shortness of breath ($p = 0.036$) significantly changed, with a decreased number of nocturia episodes after treatment on the MOS sleep scale (Table 3). Among the categories of the MOS sleep scale, the subcategories of hours of sleep/night, adequacy of sleep, and somnolence did not significantly change after treatment.

No significant treatment-related complications or clinically significant hyponatremia (serum sodium <130 mmol/L) that needed to be controlled were observed. However, 8 (13.3%) patients reported mild dizziness, mild facial edema, and fatigue. These events did not necessitate discontinuation of desmopressin therapy.

Discussion

In the present study, we evaluated the efficacy of desmopressin in elderly women with LUTS and with nocturnal polyuria simultaneously, in terms of nocturnal frequency and nocturnal urine volume. We also investigated the impact of desmopressin treatment on sleep quality using the subjective MOS sleep scale. The prevalence of nocturia significantly decreased after desmopressin treatment. The overall mean change in nocturnal frequency after 12 weeks of desmopressin treatment was 1.63 times per night. The FV chart-estimated nocturnal urine volume, NPI, and NI significantly decreased after treatment, confirming a previous

Table 2. Changes of voiding diary and the effects of desmopressin treatment on nocturnal polyuria

	Mean \pm SD		p value
	Pre-treatment	Post-treatment	
Number of nocturia episodes	3.63 \pm 1.61	2.00 \pm 1.13	0.001
Daytime urine volume (mL)	857.9 \pm 393.7	1054.4 \pm 434.9	0.001
Nocturnal urine volume (mL)	706.2 \pm 345.5	478.3 \pm 312.6	0.001
Functional bladder capacity (mL)	262.0 \pm 95.6	287.2 \pm 97.0	0.009
NPI (NUV/24 hr vol.)	0.44 \pm 0.15	0.30 \pm 0.12	0.001
NI (NUV/FVC)	2.67 \pm 0.96	1.66 \pm 0.83	0.001
NBCi (ANV-PNV)	1.95 \pm 1.46	1.33 \pm 0.67	0.001

SD: standard deviation; NPI: nocturnal polyuria index; $>35\%$: defines nocturnal polyuria; NI: nocturia index; >1.5 : nocturnal urine overproduction; NBCi: nocturnal bladder capacity index; >2 : lower bladder capacity during sleep; ANV: actual nightly voids; PNv: predicted nightly voids (NI-1); p values calculated with Student's t-test.

study about the effectiveness of desmopressin for patients with nocturia.⁷⁻¹⁰

Serum level of the antidiuretic hormone arginine vasopressin (ADH) increased and the amount of urine production decreased during night, minimizing the need to wake up to void. A significant proportion of elderly patients with nocturia lack this physiologic increase of the ADH during nighttime.^{2,7} Advancing age is associated with a decrease of nighttime excretion of ADH, so that the ADH level during daytime and nighttime becomes similar.⁷ In the present study, we included elderly women over 60 with persistent nocturnal polyuria and treated them conservatively (including behavioral modification, fluid restriction, anticholinergic treatment, and diuretics) for their nocturia.

Hvistendahl and colleagues reported that the circadian rhythm of diuresis may differ significantly between elderly population with nocturnal polyuria and young individuals during nighttime and mid-afternoon.⁸ Until now, no study has investigated the efficacy of desmopressin in elderly women with nocturnal polyuria. Older people have different circadian rhythms compared with young people; the elderly go to bed early, awaken earlier in the morning, and experience frequent awakening during sleep even in the absence of LUTS.^{9,10} Therefore, nocturia in the elderly should be interpreted differently from nocturia in young people.

Mattiasson and colleagues investigated the efficacy and safety of oral desmopressin in treating nocturia in men over 18 years old. In these men, desmopressin more than doubled the maximal bladder capacity and nocturnal urine production exceeded the maximal bladder capacity in a double-blind and placebo-controlled study.¹¹ Desmopressin reduced nocturia by $\geq 50\%$ in 34% (27/86) of patients with nocturia, whereas only 3% (2/65) had a clinical response in the placebo group. Also, the mean number of nocturnal voids decreased from 3.0 to 1.7 and from 3.2 to 2.7 in

Table 3. Changes of MOS sleep score before and after desmopressin treatment

	Pre-treatment	Post-treatment	p value
IPSS, total	20.5 ± 6.9	16.3 ± 6.7	0.001
Storage symptom	10.0 ± 2.9	7.57 ± 3.32	0.001
Voiding symptom	10.43 ± 4.5	8.73 ± 4.19	0.014
Quality of life	4.63 ± 0.80	4.13 ± 0.99	0.002
MOS sleep scale domain score			
Sleep index I	38.5 ± 12.9	33.0 ± 15.5	0.003
Hours sleep/night	6.27 ± 1.58	6.57 ± 1.29	0.080
Sleep disturbance	47.54 ± 19.3	38.2 ± 16.6	0.001
Snoring	38.6 ± 29.8	31.3 ± 21.2	0.028
Shortness of breath	18.0 ± 19.7	11.3 ± 16.2	0.036
Adequacy of sleep	47.3 ± 21.3	44.0 ± 18.3	0.264
Somnolence	35.7 ± 21.1	34.0 ± 15.7	0.435

IPSS: International Prostatic Symptom Score; MOS: Medical Outcomes Study; p values calculated with Student's t-test.

the desmopressin and placebo group, respectively.¹¹ In a double-blind, placebo-controlled study for treating nocturia in 144 women over 18, Lose and colleagues investigated the efficacy and safety of oral desmopressin.¹² They reported that 46% (33/72) of those in the desmopressin group and 7% (5/72) of those in the placebo group had a 50% or greater reduction of nocturnal voiding. The mean number of nocturnal voids, nocturnal diuresis, and ratio of nocturnal per 24 hours and nocturnal per daytime urine volumes changed significantly after desmopressin treatment.

Our present results suggest that 0.1 mg desmopressin is also effective in reducing nocturia and nocturnal urine volume in elderly women. The most significant complication of desmopressin is hyponatremia. Lose and colleagues reported several side effects in the dose titration phase up to 0.4 mg, which included headache (22%), nausea (8%), and hyponatremia (6%).¹² In our present study, there were no significant treatment-related complications or clinically significant hyponatremia (serum sodium < 130 mmol/L) that needed to be controlled. However, 8 (13.3%) patients reported mild dizziness, mild facial edema, and fatigue; these events did not necessitate the discontinuation of desmopressin therapy.

Most studies of desmopressin to reduce nocturia have demonstrated a significant decrease in nocturnal diuresis and subsequent improvement in sleep quality.^{7,11-14} Nocturnal voids can cause nighttime disturbances associated with increased sleep disorders, poor quality of sleep, and increased daytime fatigue.⁴ In the present study, we found that desmopressin therapy significantly improved subjective parameters of sleep quality; sleep index, sleep disturbance, snoring, and shortness of breath significantly changed, with a decreased number of nocturia episodes on the MOS sleep scale. We previously evaluated the impact of nocturia on subjective sleep quality in elderly male subjects, and found

that the number of nocturia episodes increased with age,¹⁵ and that nocturia was associated with negative effects on sleep quality, health-related quality of life, and bothersome symptoms.

Although nocturnal polyuria is a major contributing factor to nocturia in the elderly, not all subjects display nocturia induced by nocturnal polyuria. Elderly women with nocturia with decreased functional bladder capacity or with an over-active bladder should consider additional treatment with anticholinergics with careful monitoring of side effects and possible urinary retention. Bae and colleagues found that long-term desmopressin treatment causes gradual hyponatremia in 15 elderly men and recommended regular check of the serum sodium level at least every 6 months in elderly people.¹⁶

Our study has its limitations. For instance, the number of patients included in the study was relatively small. In addition, considering fluid overload states (such as congestive heart failure, liver disease with hypoalbuminemia, nephrotic syndrome or lower extremity venous stasis associated with nocturnal polyuria), the fluctuation of these diseases during the long study would affect the severity of nocturia. Our study could be improved by analyzing the association between alleviating nocturia and improving sleep quality to show a clear relationship between these two parameters. As a treatment outcome, we measured the disturbance of sleep evaluated by the MOS sleep measure. However the duration from starting sleep to the first void or first awakening and the hours of undisturbed sleep and other objective measures were not used to evaluate sleep quality. Further studies on the long-term efficacy and safety of desmopressin with randomized controlled protocol and large number of patients are needed.

Conclusions

Desmopressin is an effective and safe treatment for nocturnal polyuria in elderly women, when conservative treatment has failed. Sleep quality is also improved.

Competing interests: The authors declare no competing financial or personal interests.

This paper has been peer-reviewed.

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