

Voiding Dysfunction/Female Urology

Influence of Type of Nocturia and Lower Urinary Tract Symptoms on Therapeutic Outcome in Women Treated With Desmopressin

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Purpose: To investigate the type of nocturia and concomitant voiding dysfunction (VD) and the effect of desmopressin treatment on nocturia in women.

Materials and Methods: We reviewed 84 women who experienced more than 2 nocturia episodes as recorded on a pretreatment frequency volume chart and who were treated with desmopressin. All patients underwent history taking, physical examination, urinalysis, International Prostate Symptom Score assessment, completion of a urinary sensation scale, and completion of a 3 day frequency volume chart. Nocturia was divided into nocturnal polyuria (NP), reduced nocturnal bladder capacity (RNBC), and mixed type. After treatment with desmopressin, a reduction in nocturia of over 50% compared with baseline was regarded as effective.

Results: Among 84 women, the most common concomitant VD was overactive bladder (OAB, 60.7%). NP was observed in 70.2% (59/84) of the women, RNBC in 7.1% (6/84), and mixed type in 22.6% (19/84). After medication with desmopressin, 73 women (86.9%) showed a significantly reduced number of nocturia episodes (1.4 ± 1.5) compared with baseline (3.7 ± 1.3 , $p < 0.05$). Eleven women (13.1%) did not show improvement. Of the 73 women who showed improvement, 41 women showed a reduction of more than 50% over baseline, and these women had a lower baseline urgency grade.

Conclusions: In the majority of women, nocturia coexisted with other VD such as OAB. Treatment with desmopressin effectively reduced the nocturia. However, other lower urinary tract symptoms (LUTS) such as urgency may reduce the effect of desmopressin. Therefore, consideration of concomitant LUTS seems to be necessary to increase the treatment effect of desmopressin on nocturia in women.

Keywords: Deamino arginine vasopressin; Lower urinary tract symptoms; Nocturia; Women

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INTRODUCTION

Nocturia is regarded as being highly prevalent in the general population. Previous reports suggest that about two thirds of middle-aged men and women suffer from nocturia [1-4]. According to one study, the prevalence of nocturia increased at an annual rate of 7.3% in men and 3.5% in women [5]. Generally, the prevalence of nocturia is thought to be higher in men than in women, especially in the elderly population. However, nocturia is also one of the most both-

ersome lower urinary tract symptoms (LUTS) in women as well as in men. Newman and Koochaki [6] showed that 72% of women with overactive bladder (OAB) reported that nocturia was very or extremely bothersome among their LUTS. This result suggests that many more women experience nocturia than physicians may assume. The results of a meta-analysis of the prevalence of nocturia showed that 20.4% to 43.9% experienced nocturia of more than 1 episode, and 4.4% to 18% experienced nocturia of more than 2 episodes. In older women, the incidences were increased:

74.1% to 77.1% of older women showed nocturia of more than 1 episode and 28.3% to 61.5% of women showed nocturia of more than 2 episodes [7]. In addition, research on the association between age and nocturia in Korean women showed that the most common cause of nocturia was nocturnal polyuria as shown by use of 3-day frequency volume charts. Also, the incidence of nocturnal polyuria tended to increase as the women grew older [8].

Desmopressin is a synthetic analogue of antidiuretic hormone that has been used to reduce nocturia, especially nocturnal polyuria, which is an overproduction of urine at night. The clue to the use desmopressin is that secretion of antidiuretic hormone is decreased in elderly people compared with young adults; therefore, replacement of antidiuretic hormone can reduce nocturnal voids [9]. Studies of the effect of desmopressin have shown significant decreases in the number of nocturia episodes, nocturnal urine volume, and nocturnal diuresis. As a result, the first sleep period was longer and sleep quality was improved after medication with desmopressin. Adverse effects such as hyponatremia were similar between patients who received placebo and those who were treated with desmopressin according to randomized controlled trials [10-12]. For women, desmopressin can also help to reduce the nocturia caused by nocturnal polyuria, which is the most prevalent cause of nocturia in elderly women [9]. In addition, nocturia is related to various voiding problems that are common in old-age women. For example, most nocturia is associated with OAB-related storage symptoms; therefore, reduced functional bladder capacity is regarded as one of the causes of nocturia [6]. As a result, nocturia can also be improved by resolving the voiding problems causing nocturia.

Therefore, we investigated desmopressin treatment of women who complained of nocturia. We analyzed concomitant voiding dysfunction occurring with nocturia and the effect of desmopressin on nocturia retrospectively.

MATERIALS AND METHODS

We reviewed the medical records of 84 women who were treated with desmopressin 0.1 or 0.2 mg and had reported more than 2 nocturnal voids on a pretreatment frequency volume chart in the urologic outpatient clinic between January 2008 and December 2011. All patients underwent a physical examination with a comprehensive history taking, physical examination, urinalysis, International Prostate Symptom Score (IPSS), and a 3 day frequency volume chart. Urgency grade was evaluated by use of a urinary sensation scale. Patients who had neurologic diseases, previous radical pelvic surgeries, or pelvic organ prolapses were excluded from the study.

Numbers and volumes of voids over 24 hours were calculated as an average over the 3 days of the frequency volume chart. Nighttime urine production, maximal functional bladder capacity, and nocturnal index (nocturnal polyuria index [NPI] and nocturnal bladder capacity index [NBCi]) were calculated according to the International Continence

Society [13]. The definition of nocturnal polyuria differs according to age. In this study, the mean age of the women was 66.8 years old; therefore, we defined nocturnal polyuria as a nighttime urine volume of more than 33% of the total daily urine volume ($NPI > 0.33$). Reduced nocturnal bladder capacity was defined as NBCi greater than 1. Mixed-type nocturia was defined as a combination of nocturnal polyuria and reduced nocturnal bladder capacity.

All patients were started with 0.1 mg of desmopressin. After 1 month, the dose of desmopressin was increased to 0.2 mg in patients who showed no effect with desmopressin 0.1 mg. The treatment effect was evaluated in the patients who needed dose escalation after 1 month to desmopressin 0.2 mg. After treatment with desmopressin, a reduction by more than half in the number of nocturnal voids compared with baseline was regarded as effectiveness. Improvement was defined as a reduction of nocturnal voids regardless of the number compared with baseline. Statistical analysis was performed by using SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA). The data were analyzed by using the Mann Whitney U-test, and p-values < 0.05 were considered statistically significant.

RESULTS

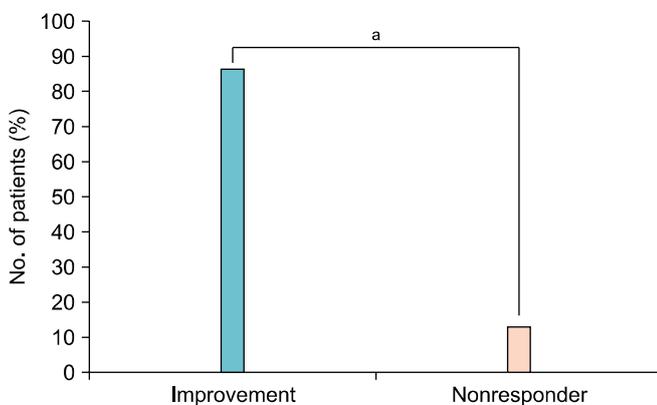
The mean patient age was 66.8 ± 10.2 years (range, 39 to 72 years). Eight patients had diabetes mellitus and 1 had a total hysterectomy owing to uterine myoma. The mean number of nocturia episodes was 3.7 ± 1.3 (range, 2 to 5). The mean total IPSS was 18.9 ± 9.7 , and the mean IPSS storage and voiding subscores were 10.1 ± 4.4 and 9.3 ± 7.1 , respectively. Among 84 women, 60.7% (51/84) complained of concomitant OAB symptoms such as frequency, urgency, or urge incontinence, and they were treated with anticholinergic agents. A total of 10.7% (9/84) took an alpha-blocker or cholinergic agent owing to concomitant female voiding dysfunction (FVD). A total of 13.1% (11/84) of patients had previously undergone anti-incontinence surgery owing to stress urinary incontinence. According to the analysis of the 3-day frequency volume chart, 70.2% (59/84) of the women had nocturnal polyuria, 7.1% (6/84) had reduced nocturnal bladder capacity, and 22.6% (19/84) had mixed type nocturia (Table 1).

After 1 month of treatment with desmopressin, the percentage of women who needed dose escalation of desmopressin from 0.1 to 0.2 mg was 39.3% (33/84). After medication with desmopressin, 73 women (86.9%) showed improvement of nocturia and the mean number of nocturia episodes (1.4 ± 1.5) was significantly reduced compared with baseline (3.7 ± 1.3) ($p < 0.05$). Among the women who showed improvement, a reduction by more than half in the number of nocturnal voids compared with baseline was observed in 41 women (48.8%). Eleven women (13.1%) did not show improvement of nocturia after medication with desmopressin (Fig. 1). Among the women who experienced improvement of nocturia, the 41 women in whom the number of nocturnal voids was reduced by more than half had a low-

TABLE 1. Baseline characteristics in women with more than 2 times of nocturia per night

Characteristic (n=84)	Value
Age (y)	66.8±10.2
Concomitant voiding dysfunction	
Overactive bladder	51 (60.7)
Female voiding dysfunction	9 (10.7)
Previous anti-incontinence surgery	11 (13.1)
Type of nocturia	
Nocturnal polyuria	59 (70.2)
Reduced nocturnal bladder capacity	6 (7.1)
Mixed	19 (22.6)

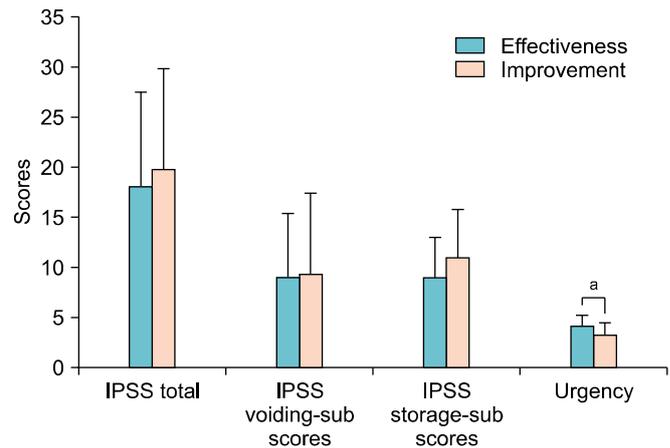
Values are presented as mean±standard deviation or number (%).

**FIG. 1.** Outcomes after medication with desmopressin 0.1 or 0.2 mg in women with nocturia. ^ap<0.05 compared with non responder.

er baseline urgency grade (3.3±1.2) by the urinary sensation scale than did the 32 women who showed improvement in nocturia but not by more than half (4.2±1.1) (p<0.05) (Fig. 2).

DISCUSSION

Among the women treated with desmopressin in this study, OAB was observed in 60.7% of women and FVD in 10.7%. Nocturia was reported by 13.1% of the women after a transobturator tape procedure. According to the 3-day frequency volume chart, 70.2% of the women had nocturnal polyuria, 7.1% had reduced nocturnal bladder capacity, and 22.6% had the mixed type of nocturnal polyuria combined with reduced nocturnal bladder capacity. Overall, the mean number of nocturia episodes was significantly reduced compared with before treatment; however, a reduction in the number of nocturia episodes by more than half was observed in 41 of the 73 women who showed improvement after medication. Furthermore, a significantly lower baseline urgency grade was observed in the women in whom nocturia was reduced by more than half than in the women showing improvement of nocturia but not by more

**FIG. 2.** Comparison of lower urinary tract symptoms between the women showed more than 50% reduction of nocturia (effectiveness) and women showed reduction of nocturia but not more than 50% (improvement). IPSS, International Prostate Symptom Scores. Urgency grade was evaluated by use of a urinary sensation scale. ^ap<0.05 compared with women showed reduction of nocturia but not more than 50%.

than half after treatment with desmopressin.

In general, nocturia is well known to be a multifactorial disease that is also related to LUTS. OAB is a common urologic problem. The prevalence is reported to be 16% to 54.5% among community-dwelling women, and the symptom of nocturia is included in the symptoms complex of OAB [14-16]. In this study, OAB was observed in 60.7% of the women who were treated with desmopressin. The reason for this relatively high ratio might be the inclusion of patients who visited a tertiary hospital. The cause of nocturia related with OAB is related to impairment of the storage function of the bladder; therefore, anticholinergic therapy to relieve OAB symptoms can decrease nocturia [17]. However, some patients do not benefit from OAB treatment alone [18].

In this study, 60.7% of women had OAB and they also complained of nocturia of more than 2 times even after anticholinergic treatment. We suspect that this finding may be because the majority of patients with OAB had concomitant nocturnal polyuria. In addition, we observed that the portion of nocturnal polyuria is greater if women with both nocturnal polyuria only and those with the mixed type are included. Nocturnal polyuria can occur as the result of excessive nighttime urine production despite normal 24-hour urine output in association with impaired secretion of arginine vasopressin. The prevalence of nocturnal polyuria has been reported to be up to 82.9%, and it is regarded as the most common cause of nocturia [19-21]. According to a study of age-related changes in nocturia in women over 20 years, 40.8% of the women showed nocturnal polyuria, and the ratio in women over 60 years was 46.7% [8]. Compared with the previous study, more women (66.7%) in the present study were assigned to the nocturnal polyuria group by the 3-day frequency volume chart. This

difference might be the result of differences in the study subjects. We studied older women (mean age, 66.8±10.2 years) than in the previous report (57.2±11.8 years) and included women complaining of more frequent nocturia (more than 2 voids per night) compared with the previous study (at least 1 void per night). These findings suggest that nocturnal polyuria is a common cause of nocturia, especially in an older population.

Desmopressin is an effective medicine for relieving nocturia due to nocturnal polyuria. According to a long-term study by Lose et al. [22], the percentage of the study group showing a reduction in nocturia of more than half of the baseline number was 46% at 3 weeks, and this figure increased to 67% at 12 months of desmopressin treatment. Another study examined the effect of desmopressin in women with nocturia of more than 2 times and a nocturia index > 1 according to a frequency volume chart. A score of > 1 on the nocturia index suggests increasing nocturnal urine volume; therefore, the cause of nocturia in patients showing an increase in the nocturia index can be regarded as nocturnal polyuria. After 3 weeks of medication, the authors observed that nocturia was reduced by half or more in 46% of the women [12]. In the present study, 48.8% (41/84) of women experienced a reduction in the number of nocturia episodes of more than half after desmopressin 0.1 or 0.2 mg, and nocturnal polyuria was observed in 58.5% (24/41) of them. In addition, 40.7% (24/59) of the women with nocturnal polyuria showed a reduction in nocturia of more than half after medication with desmopressin. This result is similar to a previous report by Lose et al. [12]. Therefore, we also noticed the effect of desmopressin on women with nocturnal polyuria.

On the other hand, 38.1% (32/84) of the women showed a reduction in nocturia that was not more than half of the baseline value after treatment with desmopressin. The difference between these women and those in whom nocturia was reduced by more than half seemed to be the baseline LUTS, especially urgency. The women who showed a reduction in nocturia that was not more than half of baseline complained of more severe urgency, which may have been the reason for the decrease in the treatment effect. This result suggests that attention should be paid to other LUTS to increase the treatment effect in patients with nocturia, because common voiding dysfunction like OAB is usually combined with nocturia.

In addition, there were women who complained of voiding problems other than OAB in this study. A total of 10.7% of women were treated for FVD as well as nocturia. The women complaining of voiding symptoms, low maximal flow rate, and increased postvoid residual urine volume were regarded as having FVD [23]. Therefore, physicians should consider FVD if women with nocturia have symptoms and signs of voiding difficulties. Among the women treated with desmopressin, 13.1% of the women had previously undergone anti-incontinence surgery. Concern about nocturia seems to be necessary after treatment of stress urinary incontinence, because nocturia can be per-

sistent or newly developed regardless of the stress urinary incontinence.

Although the results of this study might indicate an influence of LUTS on the treatment outcome of desmopressin in women with nocturia, this study had some limitations. First, it was an uncontrolled, retrospective study and thus the therapeutic effect of desmopressin was not confirmed in the combined medication or anti-incontinence surgery group. Second, the number of subjects in this study was small, and therefore further evaluation is necessary in a large number of women with nocturia and other voiding dysfunction.

CONCLUSIONS

The majority of women showed nocturia and other voiding dysfunction such as OAB concurrently. Regardless of the type of nocturia as shown by the frequency volume chart, treatment with desmopressin can effectively reduce nocturia. However, women complaining of severe urgency showed a lesser treatment effect. Therefore, consideration of LUTS other than nocturia is needed to increase the treatment effect of desmopressin on nocturia in women.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. Middelkoop HA, Smilde-van den Doel DA, Neven AK, Kamphuisen HA, Springer CP. Subjective sleep characteristics of 1,485 males and females aged 50-93: effects of sex and age, and factors related to self-evaluated quality of sleep. *J Gerontol A Biol Sci Med Sci* 1996;51:M108-15.
2. Yoshimura K, Terada N, Matsui Y, Terai A, Kinukawa N, Arai Y. Prevalence of and risk factors for nocturia: analysis of a health screening program. *Int J Urol* 2004;11:282-7.
3. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *Eur Urol* 2006;50:1306-14.
4. Yoo SS, Shim BS, Lee DH, Lee HW, Yoon H. Correlation between nocturia and sleep: a questionnaire based analysis. *Korean J Urol* 2010;51:757-62.
5. Tikkinen KA, Tammela TL, Huhtala H, Auvinen A. Is nocturia equally common among men and women? A population based study in Finland. *J Urol* 2006;175:596-600.
6. Newman DK, Koochaki PE. Characteristics and impact of interrupted sleep in women with overactive bladder. *Urol Nurs* 2011; 31:304-12.
7. Bosch JL, Weiss JP. The prevalence and causes of nocturia. *J Urol* 2010;184:440-6.
8. Kim SO, Kim JS, Kim HS, Hwang EC, Oh KJ, Kwon D, et al. Age related change of nocturia in women. *Int Neurourol J* 2010;14: 245-9.
9. Burgio KL, Johnson TM 2nd, Goode PS, Markland AD, Richter HE, Roth DL, et al. Prevalence and correlates of nocturia in community-dwelling older adults. *J Am Geriatr Soc* 2010;58:861-6.
10. van Kerrebroeck P, Rezapour M, Cortesse A, Thuroff J, Riis A, Nørgaard JP. Desmopressin in the treatment of nocturia: a dou-

- ble-blind, placebo-controlled study. *Eur Urol* 2007;52:221-9.
11. Mattiasson A, Abrams P, Van Kerrebroeck P, Walter S, Weiss J. Efficacy of desmopressin in the treatment of nocturia: a double-blind placebo-controlled study in men. *BJU Int* 2002;89:855-62.
 12. Lose G, Lalos O, Freeman RM, van Kerrebroeck P; Nocturia Study Group. Efficacy of desmopressin (Minirin) in the treatment of nocturia: a double-blind placebo-controlled study in women. *Am J Obstet Gynecol* 2003;189:1106-13.
 13. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002;21:167-78.
 14. Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol* 2003;20:327-36.
 15. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int* 2001;87:760-6.
 16. Irwin DE, Abrams P, Milsom I, Kopp Z, Reilly K; EPIC Study Group. Understanding the elements of overactive bladder: questions raised by the EPIC study. *BJU Int* 2008;101:1381-7.
 17. Rackley R, Weiss JP, Rovner ES, Wang JT, Guan Z; 037 Study Group. Nighttime dosing with tolterodine reduces overactive bladder-related nocturnal micturitions in patients with overactive bladder and nocturia. *Urology* 2006;67:731-6.
 18. Smith AL, Wein AJ. Outcomes of pharmacological management of nocturia with non-antidiuretic agents: does statistically significant equal clinically significant? *BJU Int* 2011;107:1550-4.
 19. Chang SC, Lin AT, Chen KK, Chang LS. Multifactorial nature of male nocturia. *Urology* 2006;67:541-4.
 20. Klingler HC, Heidler H, Madersbacher H, Primus G. Nocturia: an Austrian study on the multifactorial etiology of this symptom. *Neurourol Urodyn* 2009;28:427-31.
 21. Weiss JP, van Kerrebroeck PE, Klein BM, Norgaard JP. Excessive nocturnal urine production is a major contributing factor to the etiology of nocturia. *J Urol* 2011;186:1358-63.
 22. Lose G, Mattiasson A, Walter S, Lalos O, van Kerrebroeck P, Abrams P, et al. Clinical experiences with desmopressin for long-term treatment of nocturia. *J Urol* 2004;172:1021-5.
 23. Robinson D, Staskin D, Laterza RM, Koelbl H. Defining female voiding dysfunction: ICI-RS 2011. *Neurourol Urodyn* 2012;31:313-6.