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Original Article

Efficacy of desmopressin in treatment of nocturia in elderly men

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Abstract

BACKGROUND: Nocturia may be due to urological and non-urological diseases and some of the possible underlying non-urological diseases may be life-threatening. We investigated the efficacy and safety of lowest dose of oral desmopressin in treatment of nocturia in elderly men.

METHODS: 60 old men referring to urology clinic of Imam Reza hospital in Tehran, Iran from 2008-2009 for treatment of nocturia were included in a double-blind placebo-controlled study. Patients were randomly divided into 2 study groups (30 patients in each group). Care was taken to match the patients of the 2 groups by age and clinical criteria. They complained of about 2 voids per night. We divided the patients into 2 study groups. Patients belonging to group A (n = 30) received placebo and patients of group B (n = 30) received 0.1 mg desmopressin at bed time for 8 weeks. Patients were assessed after 4 and 8 weeks of treatment. The means were compared using paired sample t-test and chi-square test for time of nocturia before and after treatments and also between the two groups. ANOVA test was used for assessement of statistical differences between outcomes of the two groups.

RESULTS: Mean number of nocturia before and after receiving desmopressin were 2.6 and 1.6 respectively which differed significantly ($p < 0.001$). Mean number of nocturia before and after receiving placebo were 2.5 and 2.3 respectively with no significant difference ($p = 0.344$). After 4 weeks of treatment with desmopressin, 17 patients (56.7%) had less than 2 voids, 5 patients (16.7%) had 2 voids and 8 (26.7%) had more than 2 voids per night ($p < 0.05$). After 8 weeks, patients were evaluated and it was noticed that in group B, 4 patients (13.3%) had 2 voids, 24 (80%) had less than 2 voids and 2 patients (6.7%) had more than 2 voids per night ($p = 0.004$).

CONCLUSIONS: Oral administration of desmopressin is an effective and well-tolerated treatment for nocturia in elderly men.

KEYWORDS: Aged, Antidiuretic Agents, Deamino Arginine Vasopressin, Desmopressin, Diuretics, Muscarinic Antagonists, Nocturia, Nocturnal Polyuria.

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Previously nocturia is considered as an irritative symptom of benign prostatic hyperplasia (BPH) though nocturia and is an unresponsive symptom to various modalities of BPH treatment. Nocturia is a highly prevalent condition and its symptoms do not differ in men and women quantitatively or qualitatively.[1] Nocturia causes insomnia or sleep interruption in adult men, which has a negative impact on quality of life (QoL) and quality of sleep (QoS).[2]

Nocturia is defined as increased nocturnal urine output (nocturnal polyuria) and/or diminished nocturnal bladder capacity[3] with a mean of 2.5 or more episodes per night. Nocturia occurs in about 70% of people aged > 65 years and by the age of 90, 90% of people are affected.[4] Nocturia index increases significantly with age ($p < 0.0001$) and values are significantly higher among men than women for all age groups ($p = 0.0064$). Nocturnal polyuria index increases significantly with age ($p < 0.0001$) and no gender differences are reported.[3]

Nocturia is caused due to various factors

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like behavioral or environmental and pathologic conditions including lower urinary tract obstruction, anxiety or primary sleep disorders, sleep apnea, cardiovascular diseases, and diabetes mellitus.[5] Nocturia may be caused by combination of these and even other conditions may be attributed including nocturnal polyuria, reduced nocturnal or global bladder capacity, global 24-hour polyuria, or a combination of these factors. Nocturia has been only recently classified on the basis of its etiology and pathogenesis.[5]

Nocturia may be due to urological and non-urological diseases and some of the possible underlying non-urological diseases may be life-threatening.[6] Although several related factors are identified, none account for a substantial proportion of the population burden, indicating the multifactorial etiology of nocturia is found.[7]

The factors with the great impact at the population level are urinary urgency, benign prostatic hyperplasia, and snoring for men, and overweight and obesity, urgency and snoring for women. In addition, prostate cancer and antidepressant use for men, coronary artery disease and diabetes for women, and restless legs syndrome and obesity for both sexes are some other related factors.[7]

Nocturia, especially in men, should be treated independent of other urinary tract symptoms. The proper diagnosis and differentiation from other underlying causes of nocturia should lead to appropriate and effective management of this problem.[8]

A disorder of the vasopressin (antidiuretic hormone) system with low or undetectable levels of vasopressin bedtime affects elderly people and may cause an increase in the nocturnal urine output, which in extreme cases accounts for 85% of the 24-hour dieresis.[9]

Alpha (1)-adrenoceptor antagonists and 5 alpha-reductase inhibitors are used in men with symptoms indicating benign prostatic hyperplasia and one of their consequences is reduction of nocturia. Antimuscarinic drugs are used to depress involuntary bladder contractions.[9]

Desmopressin, a synthetic antidiuretic hormone analogue, is currently approved for the treatment of nocturia along with nocturnal polyuria or multiple sclerosis.[10] Desmopressin is a synthetic replacement for vasopressin, the hormone that reduces urine production.[11] Desmopressin may be prescribed nasally, intravenously, or in the form of tablets. US Food and Drug Administration (FDA) regulators believe desmopressin pills are safe for bedwetting treatment of otherwise healthy patient. Desmopressin limits the outflow of amount of water in the urine. It binds to V2 receptors in renal collecting ducts, causing water reabsorption. It also stimulates release of factor VIII from endothelial cells by stimulating the V1a receptor. Desmopressin degrades slower than recombinant vasopressin, and needs less frequent administration. Moreover, it has less effect on blood pressure, while vasopressin may cause arterial hypertension. It is usually in the form of desmopressin acetate, DDAVP. Patients taking DDAVP likely stay dry 4.5 times more than those taking a placebo.[11]

Desmopressin does not cause transient or mild disorders so is safer to use.[12] Its side effects may be headache, facial flushing, nausea, hyponatremia, and seizures.[11]

In the present study, we compared the efficacy of desmopressin with placebo for the treatment of nocturia in a clinical trial, double-blind study in elderly men. The present study could have certain peculiarities that have not been considered in similar researches reported so far from Iran. To find out the tolerability of the effective dose of drug, we administered the lowest dose of desmopressin to avoid its side effects. More so, minimum dose of desmopressin (0.1 mg) was prescribed in 2 period of time (4 weeks in each period). This study was gender specific. Our patients were only men and not considering other sex. It was also age specific considering men older than 50 years.

Methods

In a double-blind, placebo-controlled study, we assessed the effect of oral dose of desmopressin bedtime by measuring changes in the number of nocturnal voids from placebo to active treatment. 93 patients were screened in urology clinic of Imam Reza hospital in Tehran, Iran during

2008-2009 to determine the number of nocturnal voids. The main inclusion criteria were voiding twice or more per night.

The main exclusion criteria were as: uncontrolled disease such as diabetes and cardiac disease, use of diuretics, hypertension, diabetes insipidus, diseases which influences medulla of kidney such as medullary cystic of kidney diseases, multiple sclerosis, urge incontinence and recently surgical treatment for BPH, known functional disease in urinary system for example neurogenic bladder. 33 patients were excluded from the study on different grounds; 20 patients were excluded because of their unwillingness to continue the treatment and 13 patients on the basis of our exclusion criteria.

60 cases fulfilled the inclusion criteria and were enrolled for evaluation of efficacy of oral desmopressin for treatment of nocturia. Safety was evaluated on the basis of reported adverse effects. During the study, 1 hour before bedtime until 8 hours after taking of either desmopressin or placebo, patients drank only to satisfy their thirst, avoiding liquids with a diuretic effect. In case of observing any side effect of the drug, patient was excluded from the study. A consent form was filled by every patient.

The mean age of patients was 63.38 years with standard deviation of 11.82. They were divided randomly into 2 study groups (30 patients in each group). Care was taken to match the patients of the 2 groups by age and clinical criteria (Table 1).

Patients of group B were treated with 0.1 mg desmopressin (Ferring Co, Swiss) at bed time and patients of group A received placebo (Abidi Daru Co, Iran). Outcome was evaluated in 3 periods (before treatment, at intervals of 4 and 8 weeks after treatment).

At last, patients were evaluated considering 3 aspects of nocturia i.e. number of voids (2, < 2, and > 2 episodes), mean number of nocturia, and mean duration of the first sleep period. Safety was evaluated from reported adverse events. The sleep quality was assessed using a quality-of-life questionnaire administered by urological societies, completed by patients before and after the interventions.

Statistical differences between outcomes of the two groups revealed that differences were significant between the 2 treatment regiments. The means were compared using paired sample t-test and chi-square test for time of nocturia before and after treatments and also between the two groups.

Results

Nocturia has a negative impact on quality of life, affecting morbidity and mortality.[13] Patient's age and certain other characteristics of each group are shown in table 1. In the present study as is demonstrated in Table-1, our patients had underlying diseases both related and unrelated to nocturia which were considered while grouping them.

Results indicate that after 4 weeks of treatment in the desmopressin group 5 patients (16.7%) had 2 voids, 17 (56.7%) patients less than 2 voids and 8 patients (26.7%) had more than 2 voids/night ($p < 0.05$). In the placebo group 8 patients (26.6%) had 2 voids, 11patients (36.7%) had less than 2 voids and 11patients (36.7%) had more than 2 voids/night ($p = 0.291$).

Table 1. Demography of the study cases

Grouping	No. in Each group	Mean age (SD) year	Diabetes Mellitus	Renal disease	Hypertension	Cardiac disease	Anxiety disorder	Neurologic disease	Drug using	Diet	Other diseases
Group A (Placebo)	30	64.26 (10.46)	8 (13)	17 (28.8)	23 (38.3)	20 (33.3)	18 (30)	13 (21.7)	16 (26.7)	10 (16.7)	9 (15)
Group B (Desmopressin)	30	63.33 (13.21)	3 (10)	8 (27.6)	13 (43.3)	8 (26.7)	7 (23.3)	7 (23.3)	8 (26.7)	4 (13.3)	5 (16.7)

The patients of the 2 groups matched by age and clinical criteria. No significant difference is observed between the two groups ($p < 0.05$).

Table 2. Frequency of nocturia in the study cases before and after treatment

Grouping	No. in each group	Mean age	No. of voids per night pre treatment			No. of voids pernight 4 weeks post treatment				No. of voids per night 8 weeks post treatment			
			> 2	2	< 2	> 2	2	< 2	P value	>2	2	< 2	P value
Group A (Placebo)	30	64.26	**4**	**26**	**0**	**11**	**8**	**11**	**0.291**	**11**	**2**	**15**	**> 0.05**
Group B (Desmopressin)	30	63.33	**7**	**23**	**0**	**8**	**5**	**17**	**< 0.05**	**2**	**4**	**24**	**0.004**

There is a significant difference between the number of nocturia after 4 and 8weeks treatment in two groups (p <0.05)

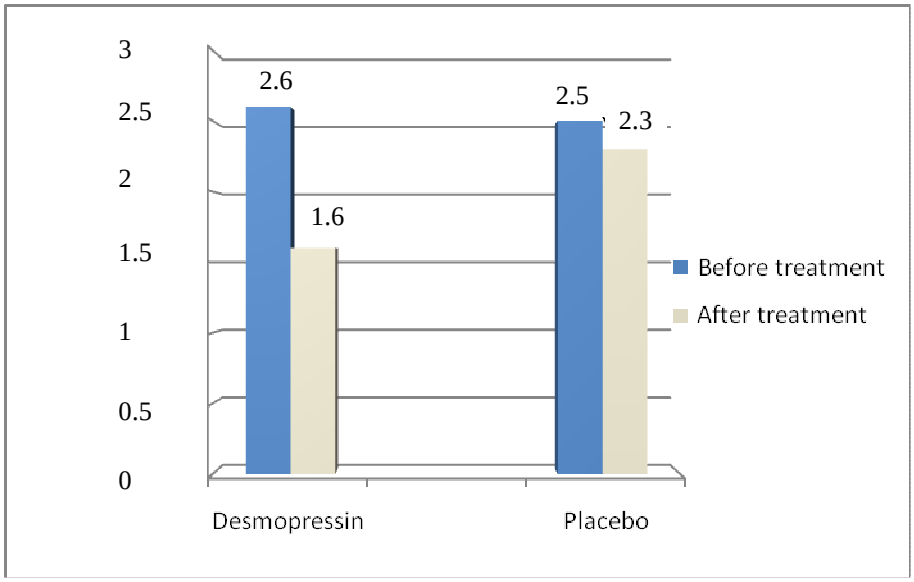

Figure 1. Mean number of nocturia before and after treatment with desmopressin and placebo

D: desmopressin, Pl: placebo

Mean number of nocturia before and after treatment with desmopressin and placebo were 2.6 to 1.6 and 2.5 to 2.3 respectively which with paired sample t test reveals significant decrease in desmopressin (p < 0.001) and insignificant decreased in placebo group (p = 0.344)

After 8 weeks, in placebo group 2 patients (6.7%) voided twice, 15 patients (50%) less than 2 and 13 patients (43.3%) more than 2 times per night (p > 0.05). In desmopressin group, 4 patients (13.3%) had 2 voids, 24 patients (80%) had less than 2 and 2 cases (6.7%) had more than 2 voids per night (p = 0.004) (Table 2).

The mean duration of the first sleep period increased by 69% (from 2 to 4 h) in the desmopressin group, compared with an increase of 20% (from 2.5 to 3 hours) in the placebo group (p < 0.01). Sleep quality in 8 weeks after treatment improved 80% (24 men) and 56.7% (17 men) in desmopressin and placebo groups respectively (p < 0.05). According to patients' opinions, duration of their first sleep period increased which led to increase in their sleep quality.

No serious drug side effect was observed in our cases.

The mean number of nocturia before and after treatment with desmopressin was 2.6 and 1.6 respectively; using paired sample test, significant decrease was noticed (p < 0.001). But the mean number of nocturia before and after placebo usage was 2.5 and 2.3 that did not differ significantly (p = 0.344). Also, there was significant difference between the mean numbers of nocturia after drugs between two groups (2.3 versus 1.6; p < 0.05) (Figure 1).

Discussion

Nocturia is a common symptom that affects the quality of sleep leading to morbidity and mortality. It is caused by a range of urological conditions and non-urological diseases.[6]

In the present study, 60 men within the age of 50 to 78 years completed our protocol in a double-blind study. This study was gender specific as our patients are only men and not considering other sex. It is also age specific considering men older than 50 years. The patients´ mean age were 63.38 ± 11.82 years and had 2 to 4 voids with mean of 2.6 voids per night.

Proper diagnosis depends on a clear understanding of its underlying etiology. Addressing conditions that contributes to nocturia is the first step for an effective treatment. Table 2 shows the underlying diseases of our study cases which may be related to nocturia.

Lifestyle and behavioral changes may be helpful in some individuals, but for many pharmacotherapies is the only option. Urological treatment includes alpha-adrenoceptor antagonists, muscarinic receptor antagonists, and vasopressin receptor agonists.[6]

Alpha (1)-adrenoceptor antagonists and 5 alpha-reductase inhibitors are usually used for treating men suffering from benign prostatic hyperplasia, with one of its consequences being reduction of nocturia.[9] Desmopressin tablets provide effective and well-tolerated treatment for nocturia.[14,15] In the present work also desmopressin tablet (0.1 mg/night for 8 weeks) was prescribed for the treatment. Compared with placebo, it resulted in reduction of nocturnal voiding frequency upto 56.7%, 69% increase in duration of the first sleep period of our patients, and improving up to 80% in sleep quality of 24 patients. Statistically significant reduction in mean number of nocturnal voids (i.e. from 2.6 to 1.6) was noticed.

Van Kerrebroeck et al stated that: "desmopressin tablets (0.1, 0.2, or 0.4 mg dose) in a 3-week period chould show sufficient response (≥ 20% reduction in nocturnal dieresis".[14] Kuo also treated patients with nocturia with three or more times a night and nocturnal polyuria refractory to medication with oral desmopressin 0.1 mg at bedtime for 4 weeks.[16]

Mattiasson et al in a double-blind study on 151 patients treated for 3-week with desmopressin concluded that the mean number of nocturnal voids decreased from 3.0 to 1.7 and from 3.2 to 2.7, respectively, reflecting a mean decrease of 43% and 12% ($p < 0.001$).[17] According to Mattiasson et al:" mean duration of the first sleep period increased by 59% (from 2.7 to 4.5 hours) in the desmopressin group, compared with an increase of 21% (from 2.5 to 2.9 hours) in the placebo group ($p < 0.001$). The mean nocturnal diuresis decreased by 36% (from 1.5 to 0.9 ml/min) in the desmopressin group and by 6% (from 1.7 to 1.5 ml/min) in the placebo group ($p < 0.001$). The mean ratio of night/24-h urine volume decreased by 23% and 1% ($p < 0.001$), and the mean ratio of night/day urine volume decreased by 27% and increased by 3% ($p < 0.001$) for the desmopressin and placebo groups, respectively".[17] In our study, the mean number of nocturnal voids decreased from 2.6 to 1.6 and from 2.5 to 2.3 in desmopressin and placebo groups respectively. The sleep quality also improved to the extent of 80% in desmopressin group.

There seems to be a relationship between the dose of desmopressin and the incidence of adverse events; although desmopressin lowers the nocturnal diuresis and the number of nocturnal voids yet it may cause adverse effects.[18]

Hvistendahl et al investigated the pharmacokinetic profile of oral desmopressin 400 microgram in 24 elderly patients with nocturia in Denmark, and observed the number of nocturia voids and nocturnal diuresis were half of that with placebo.[18] The time to the first nocturnal void was almost doubled compared with placebo. There seems to be a relationship between gender, plasma level of desmopressin, and the incidence of adverse events.

Vaughan et al conducted a randomized, controlled trial study implementing a multicomponent behavioural intervention combined with drug(s) in old men bothered from noctu-

ria. They reduced nocturia frequency and time to initiate sleep within 4 weeks.[19]

Vaughan et al treated patients with nocturia three or more times a night and nocturnal polyuria refractory to medication with oral desmopressin 0.1 mg at bedtime for 4 weeks. 20 patients (66.7%) reported a good response with both reduced nocturnal frequency ($p < 0.001$) and urine volume ($p < 0.0001$) and five patients (16.7%) reported side effects including hyponatremia in one case.[19]

In a study conducted in Italy by Nappo et al, only 2.7% of patients presented side-effect including headache, rhinitis, epistaxis, irritability, and abdominal pain.[20] In another study, no serious side-effect and in particular, no cases of symptomatic or asymptomatic hyponatremia were reported.[12] The present study consisted of only old men with the mean age of 63.38 years who received 0.1 mg desmopressin at bed time in two periods of 4 weeks. The mean number of nocturia before and after desmopressin were 2.6 and 1.6 which revealed significant decrease ($p < 0.001$), but mean number of nocturia before and after placebo were 2.5 and 2.3 that was not different ($p > 0.05$). This study showed that our patients had good response and good tolerance with desmopressin treatment.

Mattiasson et al also reported that some patients had adverse events; 15 patients (17%) in the desmopressin and 16 (25%) in the placebo group and most adverse events were mild.[17]

The authors of this study also prescribed oral desmopressin 0.1 mg at bedtime for 8 weeks and none of our patients showed any sign of drug side effects. In this respect our study is unique. To find out the tolerability of the effective dose of drug, we administered the lowest dose of desmopressin to avoid its side effects. More so, minimum dose of desmopressin (0.1 mg) is prescribed in 2 period of time (4 weeks in each period).

In some studies,[10,21] nasal desmopressin (10 µg at bedtime) was used and resulted in reduction of the mean number of nocturnal voiding episodes by 31-54%. In these studies also desmopressin increased the initial sleep period or mean maximum period of uninterrupted sleep by approximately 2 hours. Desmopressin-related adverse events were reported from these studies which were transient and mild or moderate in severity. Hyponatraemia, headache, and edema were reported in some patients that required withdrawal from studies.[10,15,21]

In a study carried out in Japan by Okada and Arakaki, efficacy and safety of intranasal desmopressin in the treatment of nocturia due to nocturnal polyuria on 12 patients was assessed. 5 patients (41.6%) reported side effects including headache, edema, and hypothermia.[21]

US drug regulators banned treating bedwetting with desmopressin nasal sprays after two patients died and 59 other suffered seizures.[11]

Although nocturia is commonly believed to be a reasonably trivial condition; its consequences are underestimated. Quality-of-life questionnaires administered by urological societies show that nocturia scores highest for bothersomeness among all voiding dysfunctions.[22]

Not only nocturia is a bothersome symptom that interrupts the sleep and also affects the quality of life, it may cause certain other related problems like increased risk of hip fractures too. Nocturia is also an important factor for fall in elderly people; up to 10% of hip fracture is secondary to waking and rising at night to void. This condition affects both men and women and is an incidence increases with increase in age. Proper treatment of nocturia in elderly patients will improve patients sleep, thereby, reduce their risk of fall injuries and the associated consequences, improving patients' health and quality of life.[9,13] Asplund concluded in these elderly subjects the risk of hip fractures during a five-year period increased by increased nocturnal micturition and increased nocturnal urine output.[23]

To conclude, desmopressin is an effective treatment for elderly patients i.e. patients 65 years or older complaining of nocturia. Doctors should be aware of the potential side effects including hyponatremia.[16,21] The safety of desmopressin has been confirmed by many

studies conducted over the course of 20 years.[12] Desmopressin decreases nocturnal urine output in severe nocturia which were resistant to conventional BPH treatment and in women also demonstrates new perspectives in management of nocturia.[1]

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Conflict of Interests
Authors have no conflict of interests.

Authors' Contributions
BR was the proposal owner, coordinated the study, and managed the patients. NA was actively involved in searching the internet sites for literature and prepared the manuscript. SS assisted in the design of the study. All authors have read and approved the content of this manuscript.

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