Comparing the Effectiveness of Intranasal Desmopressin and Doxazosin in Men with Nocturia: A Pilot Randomized Clinical Trial

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Purpose: We aimed to compare the effectiveness of intranasal desmopressin and doxazosin treatments in patients with nocturia and benign prostatic hyperplasia (BPH).

Material and Methods: Thirty one men with BPH and three or more episodes of nocturia were randomized to receive 2 mg doxazosin at night for two weeks increasing to 4 mg for a further two weeks versus 20 μg intranasal desmopressin at night. For all patients, number of nocturia, urinary flow rate, residual urine volume and quality of life score were checked. Outcomes were measured at two months. The comparison of before and after treatment changes between the groups were done by student's *t*-test.

Results: In doxazosin group, mean number of nocturia were 3.2 ± 0.4 (3-4 times) times per night and 1.2 ± 0.8 (0-3 times) times per night before and after treatment, respectively. In desmopressin group, mean number of nocturia were 3.4 ± 0.5 (3-4 times) and 1.5 ± 0.6 (1-3 times) times per night before and after treatment, respectively. In doxazosin group, mean residual urine volumes were 44.3 ± 35.9 ml (range 0-120 ml) and 23.1 ± 18.8 ml (range 0-50 ml) before and after treatment, respectively. In desmopressin group, mean residual urine volumes were 36.6 ± 32.4 ml (range 0-120 ml) and 14.0 ± 26.9 ml (range 0-90 ml) before and after treatment, respectively. Improvements in number of nocturia, residual urine volume, quality of life scores and peak urinary flow rates weren't statistically significant between two groups, whereas change in international prostate symptom score (IPSS) score was more significant in doxazosin group.

Conclusion: Intranasal desmopressin, is an effective symptomatic treatment of men with BPH complaining of nocturia, as well as doxazosin treatment.

Key Words: desmopressin; prostatic hyperplasia; drug therapy; quality of life

INTRODUCTION

Nocturia is one of the most common cause of insomnia, negatively affecting the quality of life in elderly population.[1-3] In the past, bladder and prostate diseases were regarded as the cause of nocturia. But today, it is recognized that nocturia can also be caused by excessive urine production, nocturnal detrusor hyperactivity, diminished functional bladder capacity and lower urinary tract abnormalities.[4-7] Aging is associated with increased prevalence of BPH and decreased nocturnal release of antidiuretic hormone.[8,9] As reported in the literature, desmopressin and alpha-blocker therapy significantly decreased symptoms of nocturia.[10-13] The aim of the study is to compare the effect of intranasal desmopressin to that of alpha blockers in reduction of IPSS score and reduction of post void residual urine as much as to compare pre and post intervention, the effect of intranasal desmopressin on nocturnal voiding frequency.

In this study the primary outcome variable was the frequency of nocturia. Secondary outcome variables were residual urine volume and the International Prostate Symptom Score (IPSS). We were interested in the comparison between desmopressin as change from baseline and between desmopressin and doxazosin, an alpha blocker.

MATERIAL AND METHODS

Our study was a preliminary (pilot) study to evaluate the efficacy of doxazosin and desmopressin. Eighty four consecutive patients with advanced ages who admitted to our outpatient clinic between January 2011 and June 2011 with the complaints of lower urinary tract symptoms (LUTS) and nocturia at three or more times per night were evaluated and randomized into two groups. Subjects with pathologically diagnosed prostate cancer (6 patients), positive urine culture (18 patients), prior surgery of the bladder (2 patients), prostate (10 patients), urethra (2 patients), and additional urological pathology (1 patients-trauma) were excluded. Besides, patients who do not attend treatment properly (14 patients) excluded from the study. The remaining 31 patients (16 patients group 1 and 15 patients group 2) were included in the study.

Number of nocturia, residual urine volume, urinary flow rate, IPSS symptom scores and quality of life scores were determined for all patients. Also, serum total and free prostate specific antigen (PSA) levels, urinalysis, urine culture, digital rectal examination (DRE) were performed.

Table 1. Mean values of age, serum total and free prostate specific antigen (PSA) in two groups.

	Group 1	Group 2	P value
Mean age (years)	58.1 ± 7.8	57.7 ± 9,8	.903
Mean total-PSA (ng/ml)	1.8 ± 1.4	2.6 ± 3.9	.800
Mean free-PSA (ng/ml))	0.5 ± 0.3	0.7 ± 0.6	.545

We used 7-item IPSS symptom score for symptom scoring and the eighth question in the IPSS form for quality of life scoring. Besides, the amount of residual urine was measured by bladder catheterization and peak urinary flow rate by an uroflowmetry device. The number of nocturia was assessed by the 7th question in IPSS form.

Each patient were performed transrectal ultrasonography (TRUS) in order to evaluate the morphology and volume of prostate and to perform needle biopsy, if necessary. Patients with PSA above 4 ng/ml or suspicious digital examination findings were done TRUS guided needle biopsy. All patients were filled information form and our study was approved by ethical committee. Patients in the first group were given 2 mg doxazosin orally before bedtime for two weeks, and doxazosin was continued in 4 mg dose orally before bedtime in the following days after two weeks. The second group were given 20 μg intranasal desmopressin before bedtime. After two months, all patients were readmitted for controls and urine culture, number of nocturia, IPSS scoring, urinary flow rate and residual urine determination were repeated. All patients were also questioned for side effects.

Statistical Analysis

In each group, the difference between peak urinary flow rate and IPSS values before and after treatment were analyzed by paired samples t-test. Non-parametric tests were used to analyze life quality score, number of nocturia and residual urine differences. The comparison of before and after treat-

Table 2. Mean values of residual urine volume, quality of life score, IPSS score, peak urinary flow rate, and number of nocturia before and after treatment in both groups.

	Group 1 (Doxazosin)			Group 2 (Desmopressin)		
	Before treatment	**After treatment**	***P* value**	**Before treatment**	**After treatment**	***P* value**
Number of nocturia (per night) *P* = .711[b]	3.2 ± 0.4	1.2 ± 0.8	.001[a]	3.4 ± 0.5	1.5 ± 0.6	.001[a]
Peak urinary flow rate (ml/s) P = .011[b]	13.3 ± 5.5	17.8 ± 7.8	.035[a]	17.6 ± 7.7	19.2 ± 5.3	.470[a]
IPSS score (point) *P* = .011[b]	14.6 ± 4.3	6.5 ± 2.7	.0001[a]	12.1 ± 4.9	7.4 ± 4.2	.0001[a]
Residual urine (ml) *P* = .711[b]	44.3 ± 35.9	23.1 ± 18.8	.011[a]	36.6 ± 32.4	14.0 ± 26.9	.005[a]
Quality of life score (point) *P* = .358[b]	3.6 ± 0.8	1.8 ± 0.5	.001[a]	3.4 ± 0.9	1.8 ± 0.5	.001[a]

a: The difference within each group before and after treatment
b: Change in parameters between two groups

ment changes between the groups were done by student's t-test and the comparison of before and after treatment values within the groups were done by Wilcoxon signed rank test.

RESULTS

Mean age of the patients was 58.1 ± 7.8 years (range 50-75 years) and 57.7 ± 9.8 years (range 44-79 years) in doxazosin and desmopressin groups, respectively. There were no statistically significant difference between two groups in terms of mean age. Mean serum total-PSA values and mean serum free-PSA values in the first and the second group are shown in Table 1. There were no statistically significant difference between two groups in terms of mean serum total and free-PSA.

In doxazosin group, mean number of nocturia were 3.2 ± 0.4 (3-4 times) times per night and 1.2 ± 0.8 (0-3 times) times per night before and after treatment, respectively. In desmopressin group, mean number of nocturia were 3.4 ± 0.5 (3-4 times) and 1.5 ± 0.6 (1-3 times) times per night before and after treatment, respectively. There were no statistically significant difference between two groups in terms of mean number of nocturia before and after treatment (P = .495 vs. P = .379, respectively). However, in both groups, difference between mean number of nocturia before and after treatment were found to be statistically significant (P = .001). On the other hand, mean change in number of nocturia between two groups was not statistically significant (P = .711).

In doxazosin group, mean residual urine volumes were 44.3 ± 35.9 ml (range 0-120 ml) and 23.1 ± 18.8 ml (range 0-50 ml) before and after treatment, respectively. In desmopressin group, mean residual urine volumes were 36.6 ± 32.4 ml (range 0-120 ml) and 14.0 ± 26.9 ml (range 0-90 ml) before and after treatment, respectively. The difference between residual urine volumes within each group before and after treatment was statistically significant (P = .011 and P = .005, respectively).

Within each groups, mean quality of life scores before and after treatment were found to be statistically significant (P = .001 vs. P = .001, respectively). The difference in the mean rate of improvement in quality of life scores between two groups was not statistically significant (P= 0.358).

Within each groups, mean IPSS scores before and after treatment were found to be statistically significant (P < .001). At the end of two months, change in mean IPSS scores was greater in doxazosin group than in desmopressin group (P = .011). In doxazosin group, difference between mean urinary peak flow rates before and after treatment

were found to be statistically significant (P = .035), while not statistically significant in the second group (P = .470). On the other hand, change in mean urinary peak flow rates between two groups was not statistically significant (P = .011). No major complications occurred in study groups during treatment. At the end of two months, only one patient in doxazosin group (6.25 %) complained about dizziness and drowsiness during the first two days of treatment. In the following days the complaint of the patient disappeared. Only one patient in desmopressin group (6.66%) complained about dry mouth but the complaint was not so much severe to leave the treatment. Also in desmopressin group, severe hyponatremia was not observed.

DISCUSSION

Normally, antidiuretic hormone secretion increases at night and nocturnal urine output decreases. Reduced secretion of antidiuretic hormone at night may lead to nocturnal polyuria and nocturia.[14] Nocturia manifests itself in the form of urinating at least once a night in 72 % and three or more times a night in 24 % of elderly patient population.[15-16] In this age group, nocturnal polyuria may depend on both the changes in biological rhythm of the body and bladder outlet obstructions, detrusor overactivity, neurological causes and detrusor hyperactivity. As a result, nocturia is seen with reduced functional bladder capacity.[17-19] On the other hand, it should be noted that nocturia is also an important part of lower urinary tract symptoms of BPH. The most popular treatment of lower urinary tract symptoms and nocturia is alpha-blockers while desmopressin (DDAVP) therapy, a synthetic derivative of arginine vasopressin (ADH = antidiuretic hormone), have come up to clinical practice.[20,21]

The aim of DDAVP treatment is to substitute the lacking endogenous vasopressin, as well as in Parkinson's disease, and to contribute indirectly to eliminate nocturia symptoms.[22] After prostatectomy, 19-33 % of patients have persistent nocturia complaints. This also suggests that lower urinary tract dysfunction is not the only cause of nocturia. In these cases, other possible causes such as excessive fluid intake, diabetes mellitus, neurological diseases, renal and cardiac dysfunction, should also be evaluated.[20] In our study, patients in pure middle age group who have symptoms of BPH were included. Those with pathologically diagnosed prostate cancer, reproductive positive urine culture, diabetes mellitus, previous bladder, prostatic, urethral surgery and additional urological pathology were excluded from study.

In previous studies, it was reported that DDAVP treatment in patients with nocturnal polyuria or nocturia significantly reduced the number of nocturia. Asplund and associates gave 0.4 mg/day DDAVP orally at night to 17 patients with nocturnal polyuria for two weeks. It was reported that nocturnal urine volume reduced to 0.59 ml/min, average number of nocturia reduced to 1.1 per night, average sleep time increased by 1.4 hours, the treatment was well tolerated and no serious side effect was observed.[23] In another study, Cannon and associates observed a significant decrease in number of nocturia and nocturnal urine volume in 40µgr DDAVP-treated group than the placebo group.[24] In another study of 12 patients with intranasal DDAVP, Chancellor et al. observed a decline in average AUA symptom score index from 19 ± 6 to 12 ± 6 points and in average number of nocturia from 3.6 ± 0.5 to 1.8 ± 1.1 times per night.[25] Similarly in our study, mean number of nocturia reduced from 3.4 ± 0.5 to 1.5 ± 0.6 times per night and mean IPSS score reduced from 12.1 ± 4.9 to 7.4 ± 4.2 points this reductions were statistically significant. Additionally, we studied urinary peak flow rates and residual urine volumes.

In DDAVP group, we did not observe statistically significant improvement in maximum flow rate. However, we also detected in desmopressin group that significant reduction of nocturia provided an improvement in the life quality via prolonging the duration of uninterrupted sleep. In DDAVP group, we also observed statistically significant improvements in IPSS score, quality of life score, residual urine volume and number of nocturia, except maximum flow rate. On the other hand, we think that the positive effect of DDAVP on the number of nocturia was by reducing nocturnal urine production and similarly reducing residual urine volume. Although the patients in desmopressin group were not filled voiding diaries before and after treatment, we think that improvement in IPSS scores could be depending on the improvement in bladder storage functions.

Alpha-blocker therapy in patients with BPH increased average urinary flow rate by 20-30%, reduced symptom scores

by 20-50% and reduced residual urine volume by 29%.[26,27] Fawzy and associates detected marked improvements in Qmax and symptom scores by 88% in 41 patients treated with 8 mg doxazosin, when compared with placebo.[28] Lukacs and associates reported that α-blocker therapy provided improvements on quality of life by 30% at the third month and by 43% at the end of one year.[29] In our study, mean number of nocturia reduced from 3.2 ± 0.4 to 1.2 ± 0.8 times per night in doxazosin group and from 3.4 ± 0.5 to 1.5 ± 0.6 times per night in DDAVP group. In both groups, changes in residual urine volume, number of nocturia, quality of life score and maximum urinary flow rate were not statistically significant. However, the improvement of mean IPSS score was significantly different in doxazosin group, when compared with DDAVP group. This difference may be caused by the reducing effect of alpha-blocker treatment on bladder neck, prostatic capsule and prostatic smooth muscle tone. Our study is one of the few studies examined the intranasal form of desmopressin in treatment of nocturia and there are also few studies investigated the effect of desmopressin on residual volume.

Side effects of alpha-blocker therapy especially due to the blockade of receptors in the cardiovascular system are dizziness, syncope, postural hypotension, fatigue, asthenia, headache, flu-like syndrome, nasal congestion and accommodation disorder.[30] In our study , only one patient in doxazosin group (6.25 %) was noted to have occasional dizziness and drowsiness during the first two days of treatment. The most serious and potentially fatal side effect of desmopressin treatment is hyponatremia due to water retention seen in 12-22 % of patients. Headache, nausea, vomiting, weakness, dizziness, ataxia, or weight gain have been reported in patients with risk of hyponatremia.[31-33] In our study, one patient was noted to have dry mouth in DDAVP group, but patients declared no side effects as serious as to leave the treatment. However, serious side effects should be assessed more properly by extending the follow-up period. Limitation of this study is the small number of patients. Currently, we are establishing a similar clinical study about the effectiveness of oral form desmopressin. We cannot give you any data or make any comment about the subject, because our study is still going on.

CONCLUSION

Intranasal desmopressin treatment is a safe and effective treatment as alpha-blocker therapy in BPH patients suffering from LUTS and nocturia, with minimal side effects and maximum patient safety. Additional multi-center studies with more subjects will support the results of our study.

CONFLICT OF INTEREST

None declared.

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