DOI Number: 10.37506/v20/i1/2020/mlu/194400

Oral Desmopressin as an Add-on Therapy for Men with Benign Prostate Hyperplasia they Suffering from Persistent Nocturia

Firas Alquraishi[1] Saif H. Mohammed[1], Yasser Al-Hakeem[1]

[1]Lecturer, PhD. surgery Department, Al-Nahrain University/College of Medicine/Iraq

Abstract

Background: men with benign prostate hyperplasia suffer from urinary tract infection especially in lower part of the tract and common manifestation of this infection is nacturia. Treatment of nocturia depends mainly on α-blockers; however, these drugs have limited success in relieving this symptom. **Aims:** This study aims to assess the efficacy of desmopressin (0.2mg) as an add-on therapy with α-blockers in relieving refractory nocturia for men with BPH. **Patients and Methods**: Inclusion criteria for this prospective, non-randomized, open-label trial included men ≥60 years old with LUTS due to BPH; a total IPSS of ≥14 points; and persistent nocturia with ≥2 voids/night despite using α-blockers for at least 10 weeks prior to inclusion. Patients with diabetes mellitus, known neurogenic bladder dysfunction, uncontrolled hypertension, congestive heart failure, and those using diuretics were excluded from the study. Fifty one patients were included and categorized into two groups; those who continued on α-blocker treatment (n=22), and those for whom oral desmopressin (0.2 mg) was used as an add-on therapy (n=29). After four weeks of treatment, the International Prostate Symptom Score (IPSS), storage and voiding subs-scores, nocturia episodes, maximal flow rate ($Q_{max)}$ and bother score were measured and compared with their respective baseline values. **Results:** there were no difference significantly between the two groups in all measured demographic and clinical parameters (all *p*-values >0.05). After four weeks of treatment, the total IPSS, storage sub-score, nocturia episodes, and bother score were all significantly better in the group were desmopressin add-on (P-values ≤0.05). No significant differences were observed in the voiding sub-score and Q_{max} value between the two groups (both *p*-value >0.05). **Conclusion:** adding desmopressin to α-blockers is active therapy for men with BPH and suffering nocturia and no initial response to α-blockers.

Keywords: *nocturia, desmopressin, benign prostate hyperplasia, lower urinary tract infection*

Introduction

Benign prostatic hyperplasia is one of the most common causes of lower urinary tract symptoms (LUTS) in ageing men. BPH can cause nocturia via different mechanisms including detrusor overactivity and a high post void residual (PVR), both of which can result in decreased voiding volume and frequent voiding [(1)]. However, LUTS is not the sole cause of nocturia. Rather, nocturia is considered as a multifactorial condition and five main causes have been identified including nighttime polyuria, worldwide polyuria, decrease bladder volume, sleep problems and circadian clock illnesses [(2)]. It is very common to find a patient with more than one of these factors involved [(3)]. Nocturia is a critical condition that necessitates clinical attention. Persistent nocturia can result in chronically disturbed sleep, with a negative effect on patient's class of life (QoL) and general health. In elderly, frequent voiding during night can particularly expose the patients to slipping and fractures [(4)]. Moreover, the impact of nocturia extends beyond being a medical issue. For example, the annual direct cost of managing nocturia in Germany, including the costs of medical consultations, investigations, medicines and treatments of falls and fractures, is about 2.32 billion euros and the annual indirect costs, by loss of labor due to diminished efficiency or absence at the workplace, is about 20.76 billion euros [(5)]. The treatment approaches for nocturia usually depends on pharmacological therapy

that is assigned principally for BPH, namely α-blockers, 5α-reductase inhibitors, and anticholinergics. However, in most cases with BPH, using these drugs is not associated with satisfactory results in reducing voiding frequency [6]. Thus, this study aims to assess the efficacy of desmopressin (0.2mg) as an add-on therapy with α-blockers in relieving refractory nocturia for men with BPH.

Patients and Method

A prospective study for four weeks single center, open-label, non-blinded comparative study. Inclusion criteria were men ≥60 years old with LUTS due to BPH; a total IPSS of ≥14 points; and persistent nocturia with ≥2 voids/night despite using α-blockers for at least 10 weeks prior to inclusion. Patients with diabetes mellitus, known uncontrolled hypertension, neurogenic bladder dysfunction, congestive heart failure and those using diuretics were excluded from the study. From February 2018 to February 2019, patients who attended the Urosurgery department at Al-Imamain Al-Kadhumain Medical City in Baghdad were assessed for inclusion. After excluding ineligible cases, a total of 51 patients were included and assigned into two groups, those who remained on an α-blocker (n=22), and those who received oral desmopressin 0.2 mg add-on therapy with an α-blocker (n=29). All included patients were assessed at baseline and after four weeks for IPSS, including storage and voiding sub-scores, as well as bother scores and Qmax levels. A consent form explaining the aims of the study was obtained from all patients. The study was approved by the ethical committee of Al-Imamain Al-Kadhumain Medical City. **Statistical Analysis:** Statistical Package for Social Sciences (SPSS) was used for data analysis. Paired student t-test was used to compare means of total IPSS, voiding and storage sub-scores, and Q_{max} at baseline and 4 weeks after the onset of treatment within the same group, while independent t-test was used to compare the means between the two groups. A p-value of ≤ 0.05 was considered as significant.

Results

Baseline Characteristics of the Patients: continuous data were subjected for normality test (Shapiro Wilk test) and were found to be normally distributed. The mean age and stander deviation of the patients on α-blockers alone is (63.95 ±10.15) years compared to (62.43±10.72) years for those patients using desmopressin add-on with no significant difference (P-value = 0.607). Likewise, no significant differences between the two groups in IPSS total score, storage and voiding sub-scores, nocturia episodes, bother score, PSA level, prostate size and Q_{max} (all P-values >0.05) (Table 1).

Table 1: Baseline characteristics of patients

Variables	α-blocker alone (n=22)	Desmopressin add-on (n=29)	p-value*
Age (years)	63.95±10.15	62.43±10.72	0.607
IPSS total score	24.18±3.69	25.75±4.94	0.221
IPSS voiding sub-score	11.8±1.8	12.1±2.4	0.306
IPSS storage sub-score	13.1±1.9	13.65±2.6	0.903
Nocturia episodes	3.95±0.78	4.0±0.75	0.835
Bother score	4.64±1.0	4.52±1.05	0.685
PSA (ng/ml)	1.7±1.0	1.66±0.98	0.874
Prostate size (cm3)	52.5±13.86	54.11±12.97	0.675
Qmax (ml/s)	17.68±5.54	15.59±4.32	0.135

Data presented as mean ± SD; IPSS: international prostatic symptom score;
PSA: prostate specific antigen; Q_{max}: maximum urine flow rate
*Using independent sample t-test.

Effect of desmopressin add-on on IPSS scores, bother score, and Q_{max}:

As seen in table (2), when each treatment group was assessed separately before and after treatment, the total IPSS, storage sub-score, voiding sub-score, bother score, and nocturia episodes were significantly lower following treatment in both groups (all p-values ≤0.05). However, Q_{max} values were significantly higher only in the desmopressin add-on group (p-value=0.025). In a head-to-head comparison for the same parameters following four weeks of treatment (table 2), the mean IPSS score for the desmopressin add-on group (14.07±3.66) was significantly lower than that of α-blocker alone group (17.09±4.5), with P-value of (0.012). Similarly, desmopressin add on-treated group had a better IPSS storage sub-score compared to α-blocker alone group (6.92±1.71 vs. 7.98±2.87, P-value 0.018), with a significantly lower bother score (2.83±0.96 vs. 3.91±1.19, P-value 0.001) and a significantly less nocturia episodes (1.59±0.82 vs. 3.32±0.99, p-value 0.0001). On the other hand, there was no significant difference between the two groups in the voiding sub-score (P-value 0.366) and Q_{max} (P-value 0.074).

Table (2): Effects of desmopressin add-on on IPSS scores, sub-scores, and Q_{max}

Variables	**Status**	**α-blocker alone**	**Desmopressin add-on**	**$p^{(a)}$-value**
IPSS total score After treatment	Baseline	24.18±3.69	25.75±4.94	0.012
	17.09±4.5	14.07±3.66		
$P^{(b)}$-value		< 0.001	< 0.001	
IPSS voiding sub-score After treatment	Baseline	11.8± 1.8	12.1±2.4	0.336
	9.12±2.7	7.15±2.2		
$P^{(b)}$-value		<0.001	<0.001	
IPSS storage sub-score After treatment	Baseline	13.1± 1.9	13.65±2.6	0.018
	7.98±2.87	6.92±1.71		
$P^{(b)}$-value		<0.001	<0.001	
Nocturia episodes	Baseline	3.95±0.78	4.0±0.75	0.0001
	After treatment	3.32±0.99	1.59±0.82	
$P^{(b)}$-value		0.001	0.0001	
Bother score	Baseline	4.64±1.0	4.52±1.05	0.001
	After treatment	3.91±1.19	2.83±0.96	
$P^{(b)}$-value		0.014	0.0001	
Q_{max} (ml/s) After treatment	Baseline	17.68±5.54	15.59±4.32	0.074
	16.91±3.2	18.35±5.58		
$P^{(b)}$-value		0.289	0.025	

IPSS: International Prostate Symptom Score; Q_{max}: maximum flow rate

$p^{(a)}$: Designed using independent t-test; $p^{(b)}$: Designed using paired t-test

Discussion

For greatest knowledge, this study is the first study that show usage of desmopressin in management of patients with benign prostate hyperplasia and suffering from nocturia. The current results confirms the efficiency of desmopressin as an add-on therapy in the alleviation of nocturia through reducing the total IPSS, storage sub-score, nocturia episodes, and bother score after four weeks of treatment compared to those treated with an α-blocker alone. Several previous studies have reported similar findings.

Shin et al. (2014) enrolled 405 men with persistent nocturia due to BPH in a large prospective randomized trial to investigate the role of desmopressin (0.2 mg) as add-on therapy in reducing LUTS in those patients. It was found that the number of episodes of nocturia, nocturnal urine volume, and nocturnal index were significantly decreased using an α-blocker plus an antidiuretic agent [7]. In a cross sectional study including 136 patients, Chen et al. (2016) reported that long-term treatment with low dose desmopressin, 0.05 mg increased to 0.2 mg as required, was effective in the treatment of nocturia in Chinese patients with LUTS/BPH with or without nocturnal polyuria [6]. In another study, Kim et al. (2017) divided a total of 86 men with persistent nocturia in spite of the usage of α-blocker therapy for 8 weeks into two collections, one of this collection of patients treated with desmopressin (0.2 mg) and another collection of patients take placebo. The desmopressin added group was significantly improved when compared with placebo group in the no. of nocturnal occurrences, nighttime urine volume, entire IPSS, nocturnal polyuria index, and International Consultation on Incontinence Questionnaire score. Furthermore, the authors found that the adverse events in desmopressin add-on group were not different from that in the placebo group. Regarding QoL, no significantly differences between 2 groups in the variation of IPSS QoL score, so the International Consultation on Incontinence Questionnaire-Nocturia Module (ICIQ-N) agreed with this results that there was significant improved when used desmopressin add-on compared to the group not used it [8]. More recently, Taha et al. (2018) published a systematic review that included 3072 patients with BPH/LUTS and persistent nocturia. The study demonstrated that a combination of α-blockers and desmopressin add-on resulted in a 64.3% redused in the occurrence of nocturnal voids compared to 44.6% of patients used α-blockers a lone [9]. On the other hand, a Turkish study by Koca et al (2012), which is similar to our study, found that there was no significant difference in terms of IPSS, Q_{max}, and QoL between alfuzosin-alone and desmopressin add-on treatment after a treatment duration of three months, although both groups had a significant improvement in these parameters when compared to their baseline measurements [10]. The effect of desmopressin can be explained by the fact that in most cases nocturia is considered as an associated condition within LUTS, and accordingly treated with drugs allocated for BPH or overactive bladder. Usually, these drugs include α-blockers and (or) 5α-reductase inhibitors. However, the response to such treatment was not satisfactory in most cases which could be due to the multifactorial nature of nocturia [6]. Furthermore, nocturia can be improved by some behavioral performs such as decreasing fluid intake at bedtime, thus several non-pharmacological factors can interfere with the drug activity (Km et al., 2017). Desmopressin acetate (Minirin®) is an artificial equivalent of arginine vasopressin, alike antidiuretic action but have no vasopressor actions. Have active effects in the management of conditions with polyuria: such as primary nighttime enuresis and essential diabetes insipidus. Therefore, it can be expected to possess a dual activity when it is used as an add-on therapy beside α-blockers in reducing nocturia as well as other LUTS [11]. Collectively, these data support the use of oral desmopressin (0.2 mg) as an add-on treatment to α-blockers for the management of men with BPH/LUTS they suffering from refractory nocturia. The present study has limitations including: absence of blinding and randomization, small sample size, the lack of input from a bladder diary or from a nocturia-specific questionnaire and not addressing the side effects of desmopressin. Further studies that include women with LUTS are required to popularize the use of desmopressin as essential element for treatment of this disorder.

Conclusions

Adding desmopressin to α-blockers is active therapy for men with BPH and suffering nocturia and no initial response to α-blockers.

Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: Self-funding

References

1. Gacci M, Sebastianelli A, Spatafora P, Corona G, Serni S, De Ridder D, et al. Best practice in the management of storage symptoms in male lower urinary tract symptoms: a review of the evidence base. Therapeutic advances in urology. 2018;10(2):79-92.
2. Van Kerrebroeck P, Andersson KE. Terminology, epidemiology, etiology, and pathophysiology of nocturia. Neurourology and urodynamics. 2014;33(S1):S2-S5.
3. Andersson K-E, Van Kerrebroeck P. Pharmacotherapy for nocturia. Current urology reports. 2018;19(1):8.
4. Kim SY, Bang W, Kim M-S, Park B, Kim J-H, Choi HG. Nocturia is associated with slipping and falling. PloS one. 2017;12(1):e0169690.
5. Oelke M, Fangmeyer B, Zinke J, Witt JH. Nocturia in men with benign prostatic hyperplasia. Aktuelle Urologie. 2018;49(4):319-27.
6. Chen SL, Huang YH, Hung TW, Ou YC. Comparison of nocturia response to desmopressin treatment in elderly men with and without nocturnal polyuria in real-life practice. International journal of clinical practice. 2016;70(5):372-9.
7. Shin YS, Zhang LT, Zhao C, Kim YG, Park JK. Twelve-week, prospective, open-label, randomized trial on the effects of an anticholinergic agent or antidiuretic agent as add-on therapy to an alpha-blocker for lower urinary tract symptoms. Clinical interventions in aging. 2014;9:1021.
8. Kim JC, Cho KJ, Lee JG, Seo JT, Kim DY, Oh S-J, et al. Efficacy and safety of desmopressin add-on therapy for men with persistent nocturia on α-blocker monotherapy for lower urinary tract symptoms: a randomized, double-blind, placebo controlled study. The Journal of urology. 2017;197(2):459-64.
9. Taha D-E, Aboumarzouk OM, Shokeir AA. Oral desmopressin in nocturia with benign prostatic hyperplasia: A systematic review of the literature. Arab journal of urology. 2018;16(4):404-10.
10. Koca O, Keleş MO, Güneş M, Öztürk M, Akyüz M, Karaman M. Desmopressin in the treatment of nocturia with BPH. Turk J Urol. 2012;38(1):29-31.
11. Ahmed A-FA-M, Amin MM, Ali MM, Shalaby EA-M. Efficacy of an enuresis alarm, desmopressin, and combination therapy in the treatment of saudi children with primary monosymptomatic nocturnal enuresis. Korean journal of urology. 2013;54(11):783-90.