ISSN:0975-3583,0976-2833 VOL12,ISSUE 05,2021

Treatment of Nocturia in Patients with Benign Prostatic Hyperplasia Using Desmopressin to Alpha Blockers

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ABSTRACT

Background: Benign Prostatic Hyperplasia (BPH) is a non-cancerous enlargement of the prostate. It is a very common urological problem among ageing men and leads to lower urinary tract symptoms. The aim of the present study was to evaluate the best available medical treatment for nocturia in patients of BPH. **Patients and methods:** A prospective study included 44 male patients complaining of LUTs of BPH with nocturia were enrolled to Urology Department, Zagazig University Hospitals. They were divided randomly into 2 groups, each group include 22 patients. Group A: the patient received oral desmopressin add on tamsulosin once daily. Group B, the patient received oral tamsulosin daily. The clinical assessment was done before and after treatment (12 weeks). **Results:** No significant difference founded at before treatment regard total IPSS but group A was significantly lower regard total IPSS after treatment and both groups significantly decreased after treatment. Group A significantly associated with better improvement at all 4 domain of sleep scales (Getting to Sleep,Quality of Sleep, Awake following Sleep and Behavior Following Wakening) more than Group B significant difference between groups. **Conclusion:** Oral desmopressin added to α-blockers is well tolerated and beneficial for improving the IPSS and nocturnal symptoms. Desmopressin can be expected to possess adual activity when used as an add-on therapy beside α-blockers in reducing nocturia as well as other LUTS.
Keywords: Desmopressin, Nocturia, BPH, Alpha Blockers

INTRODUCTION

The adopted definition by the international contienence society (ICS) of nocturiais waking up at night once or more to void and being preceded and followed by sleep **(1)**. Most people with <2 voids/night have only minimal bother but when ≥2 voids/night occur nocturia may impact health-relatedquality of life (HRQoL) **(2)** and, therefore, is considered clinically relevant **(3,4)**.

Benign Prostatic Hyperplasia (BPH) is one of the most commonly cited risk factors for nocturia in the elderly, affecting almost 40% of men older than 50 years of age,88% of men 80 years of age, and nearly 100% of men 90 years of age **(5,6)**.

Nocturia is a bothersome common storage symptom associated with BPH. However, it does not fully respond to alpha-blocker therapy, probably due to its multifactorial pathophysiology. It can persist even after effective treatment of BPH,and bladder relaxing drugs such as anticholinergics, will increase bladder capacity and generally reduce urinary frequency and urgency **(7)**. Their effect on nocturia is less certain, and there is a concern about possibly contributing to slightly higher post void residuals or urinary retention in men. These drugs tend to be more effective in patients with other symptoms of overactive bladder **(8)**,therefore desmopressin therapy has been incorporated into clinical practice **(9).**

Desmopressin, a synthetic analogue of arginine vasopressin, has antidiuretic effects and leads to a significant decrease in nocturnal urine output as well as the number of nocturiaepisodes in nocturnal polyuria **(10)**.

The orally disintegrating desmopressin tablet avoids ingestion of extra fluids, overcomes swallowing difficulty,and has improved bioavailability compared to the standard tablet. The routine addition of oral desmopressin to alpha blocker therapy to improve patients' bother symptoms is questionable **(11)**.

The aim of this study is to provide best available medical treatment for nocturia in patients of BPH by evaluate the outcome. To asses quality of life parameters, compare International prostatic symptom score (IPSS) before and after use of desmopressin. Also, asses sleep quality by using leed sleep evaluation questionnaire (LSEQ) before and after use desmopressin.

PATIENTS AND METHODS

A prospective study study carried out at the department of urology, Zagazig university hospitals. Assuming the total number of patients attending was 8 cases/ month during the study period (6 months). Patients divided randomly by using computer randomization program into 2 parallel

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groups; 1st group (Group A) patients will take alpha blockers with desmopressin for 12 weeks. 2nd group(Group B) patients will take alpha blockers(oral tamsulosin 0.4mg at bedtime for 12 weeks) only.

Inclusion and exclusion criteria:

Males patients with BPH and nocturia 2 times or more / night**.** While, Cases with diabetis insipidus, uncontrolled diabetis mellitus, ploydepsia, congestive heart failure, treatment with diuretics and impaired renal function were excluded from the study.

Dose of the drug:

Desmopressin is administered orally at bedtime for 12 weeks usually beginning with 0.1 mg. Dose increase or decrease was permitted upon patient response in 1-week intervals to a maximum desmopressin dose of 0.4 mg and a minimum dose of 0.05 mg.

Clinical Assessment:

Adetailed history of the problem is required for all patient, specially history of LUTS with focus on nocturnal polyuriaby using International Prostate Symptom Score (IPSS):consisting of seven symptom questions and one Qolquestion. Bladder diary {Frequency voiding chart (FVC): done for all cases. Patients were asked to complete 3-day FV charts. They were taught how to precisely complete the FV charts by the urologist and were asked not to alter their usual fluid intake and voiding habits during the study. ICIQ-N (International Consultation on Incontinence Modular Questionnaire-Nocturia) is a questionnaire for evaluating the frequency of daytime and night time urination and impact on quality of life (QoL) and outcome of treatment in patient. is a validated questionnaire for a recall period of 4 weeks with a total of two items.

LSEQ (leeds sleep evaluation questionnaire):

The LSEQ was designed to assess changes in sleep quality over the course of a psychopharmacological treatment interventionand is a validated self –reporting instrument comprising100mm(10cm) visual analogue scale.contains 10 questions pertaining to four consecutive aspects of sleep.

Laboratory assessment:

Urine analysis; Urinalysis (dipstick or sediment) must be included in the primary evaluation of any patient presenting with LUTS to determine conditions diabetes mellitus. Serum electrolytes (Na,K) were estimated. If serum sodium concentration has remained normal and no dose adjustment is intended, patients should be informed about the symptoms of hyponatraemia. RFT;renal function may be assessed by serum creatinine.

Radiological assessment:

Abdominal and pelvic ultrasound; used to evaluate both kidneys, urinary bladder and prostate with lower cost, lower radiation dose and less side effects. Post void residue; Post-void residual (PVR) urine can be asses by transabdominal US, bladder scan or catheterisation. PVR not necessarily associated with BOO, since high volumes can be a consequence of obstruction and/or detrusor function.

Statistical analysis:

Data analyzed using Microsoft Excel software and imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance; difference and association of qualitative variable by Chi square test (X2). Differences between quantitative independent groups by t test. P value was set at <0.05 for significant results &<0.001 for high significant result.

RESULTS

This Prospectivestudy carried out on 44 male patients complaining of LUTs of BPH with nocturia. Age was distributed as 59.64±3.76 and 61.05±2.91 respectively with no significant difference between groups and Duration was distributed as 12.05±2.72 and 12.00±2.5 respectively with no significant difference and nosignificant difference at BMI between groups **(Figure 1)**.

The mean serum Na of patients at group A was 142.35No significant difference regard before treatment but at after 4 week 12 week of treatment ; group A was(mean of Na=137.68±2.033) significantly lower and significantly decreased from before to after treatmen **(Figure 2)**.

There was no significant difference between groups in both Nocturnal void before treatment (mean nocturnal void=3.64±0.64, mean nocturnal volume=38.86±12.9) as group A was significantly lower and both groups significantly changed and improved from before to after treatment **(Figure 3).**

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No significant difference founded at before treatment regard total IPSS but group A was significantly lower regard total IPSS after (12 wk) treatment and both groups significantly decreased after(12 wk) treatment (6.36±2.59 in group A and 10.55±4.13 in group B) but more in Group A **(Figure 4)**.

No significant difference founded regard mean of ICIQ-N before treatment and both groups significantly decreased in mean of ICIQ-N after treatment(12 week) butGroup A (mean=1.77±0.86) more significantly decreased **(Figure 5)**.

Group A significantly associated with better improvement at all 4 domain of sleep scales(Getting to Sleep,Quality of Sleep, Awake following Sleep and Behavior Following Wakening) more than Group B significant difference between groups regard this scale **(Table1)**.

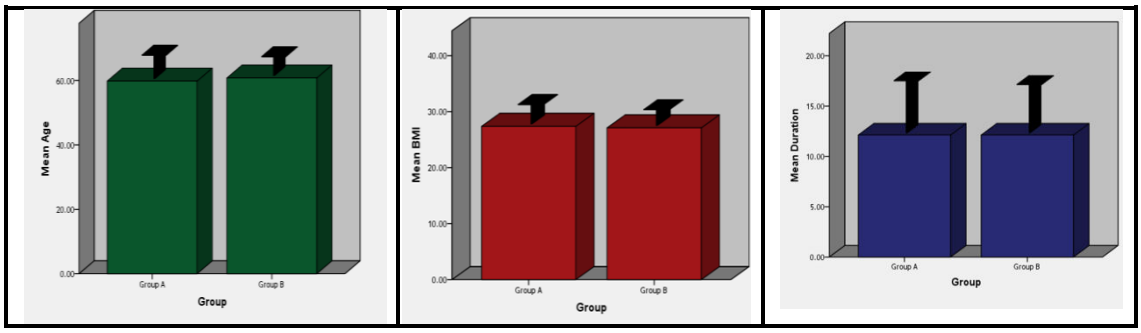

Figure (1): Mean age, BMI and duration distribution of studied groups.

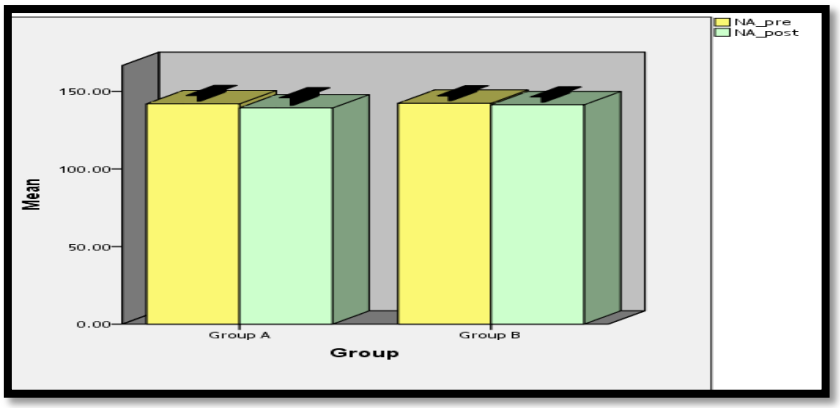

Figure (2): Serum sodium (Na) distribution before and after treatment (12weeks) between studied groups

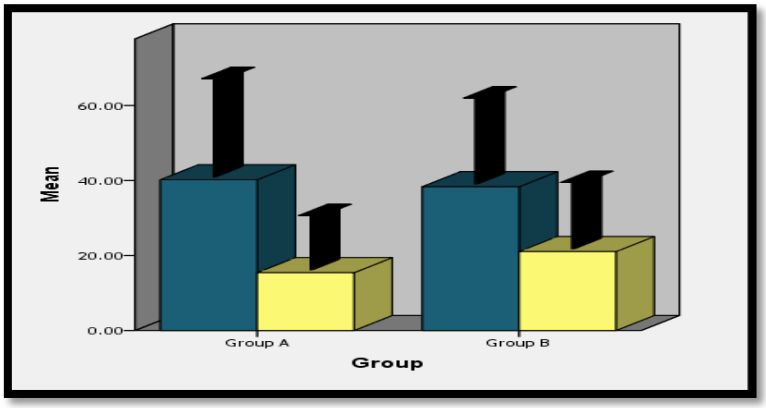

Figure (3): Nocturnal voids and volume in bladder diary before and after treatment (12weeks) distribution between studied groups

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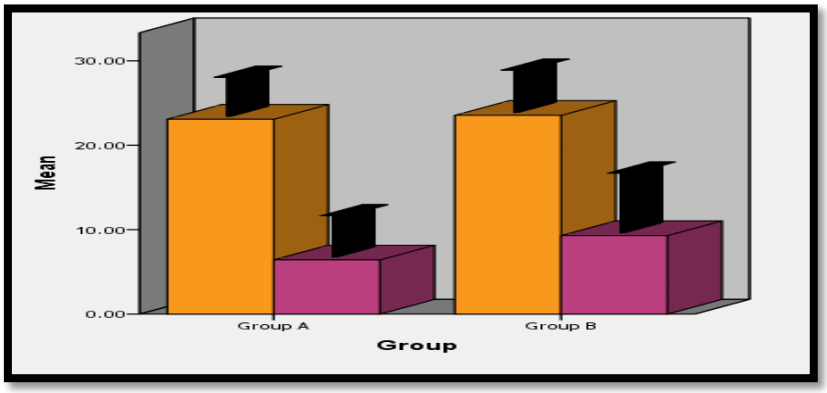

Figure (4): Total IPSS distribution before and after treatment (12weeks) between studied groups

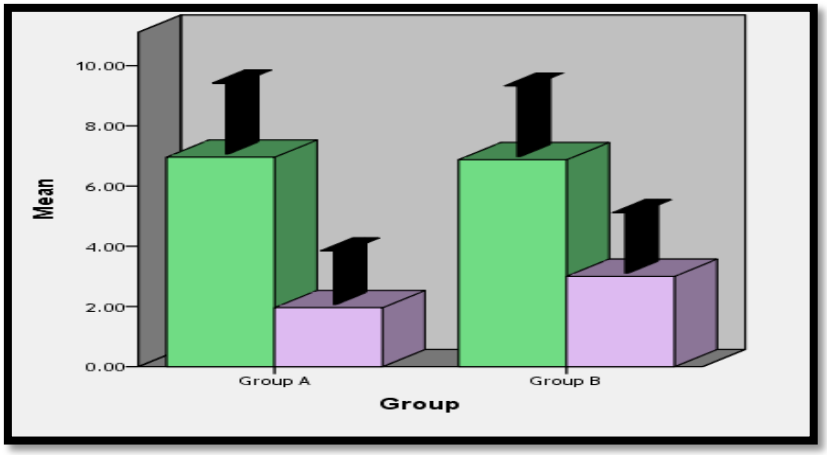

Figure (5): ICIQ-N before and after treatment distribution between studied groups

Table 1: LSEQ score after treatment distribution between groups

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	Group	N	Mean	SD	t	P
GTS1	A	22	-1.88	0.35	2.991	005.0
	B	22	-1.32	0.78		
GTS2	A	22	-1.64	0.49	2.710	010.0
	B	22	-1.14	0.71		
GTS3	A	22	-1.64	0.49	3.91	000.0
	B	22	-0.95	0.65		
GTS	A	22	-1.71	0.40	4.574	000*.0
	B	22	-1.13	0.43		
QOS1	A	22	-1.77	0.52	4.286	0.000
	B	22	-0.95	0.72		
QOS2	A	22	-1.77	0.52	2.903	0.006
	B	22	-1.18	0.79		
QOS	A	22	-1.77	0.33	4.788	0.000**
	B	22	-1.06	0.60		
AFS1	A	22	-1.77	0.42	3.818	000.0
	B	22	-1.05	0.78		
AFS2	A	24	-1.91	0.42	3.400	001.0
	B	24	-1.27	0.76		
AFS	A	24	-1.84	0.28	5.392	000***.0
	B	24	-1.15	0.52		
BFW1	A	24	-1.82	0.39	3.437	001.0
	B	24	-1.27	0.63		
BFW2	A	24	-1.64	0.58	4.264	000.0
	B	24	-0.77	0.75		
BFW3	A	24	-1.68	0.47	4.370	000.0
	B	24	-0.82	0.79		
BFW	A	24	-1.71	0.40	5.790	000****.0
	B	24	-0.95	0.46		

SD=standard ,t= t test ,P = P value LSEQ Leeds Sleep Evaluation Questionnaire, GTS—Getting to Sleep Scale 1: easier/more difficult 1,Scale 2: quicker/longer −,Scale 3: less/more sleepy – QOS-Quality of Sleep Scale 4: calmer/more restless −.Scale 5: less/more wakeful periods −AFS—Awake following Sleep <Scale 6: easier/more difficult −Scale 7: shorter/longer period , BFW—Behavior Following Wakening ,Scale 8: perception at awakening: alert/tired −Scale 9: feeling now: alert/tired −Scale 10: balance-coordination upon awakening: less/more disrupted. A reduction indicates improvement, 0 no change, and an increase deterioration

DISCUSSION:

In patients with benign prostatic hyperplasia (BPH), nocturia mostlyresults from decreased nocturnal bladder capacity, and/or detrusor overactivity that decreases functional bladder capacity **(12)**. Men with lower urinarytract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) may experience nocturia due to reduced (nocturnal) bladder capacity with or without detrusor overactivity **(13)**.

Nocturia is one of the most distressing lower urinary tract symptoms (LUTS) in men, and its prevalence in a population-based survey was reported to be up to 65% in men aged ≥40 years **(14)**. Nocturia shows a strong association with decreased quality of life (QoL) for men resulting from sleep disruption, daytime tiredness, and mood disturbance **(15)**.

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 **(16)**.

In this study 48 patients were randomly allocated in two groups, one patient withraw from study , then patients randomized into two groups ; group A include 24 patients received desmopressin and tamsulosin for 12 weeks(two patients of them escaped during the follow up of the study so the study was completed by 22 patients in group A)& group B include 23 patients receiving tamsulosin only for 12 weeks(one patients was missed during the follow up of the study so the study was

ISSN:0975-3583,0976-2833 VOL12,ISSUE 05,2021

completed by 22 patients in Groupe B). Patients in both groups were followed for 12 weeks and were evaluated at 1st week&4thweek & 12th week and on demands regarding International Prostate Symptom Score (IPSS) , IPSS-QOL , bladder diary,serum sodium, ICIQ-N (International Consultation on Incontinence Modular Questionnaire-Nocturia) and LSEQ (leeds sleep evaluation questionnaire)

Our results are in the same line with **kim et al.,(17)** investigated the efficacy of desmopressin add-on therapy in 86 men aged 40-65 years with persistent nocturia on alpha-blocker for lower urinary tract symptoms (LUTS). Baseline characteristics were similar between the two groups. Also, **Berges et al.,(18)** included total of 137 patients. The baseline demographics and disease characteristics of all trial participants. Mean age was 62.6 years, median duration since first LUTS/BPH diagnosis was 35 weeks.

Our study concur Desmopressin therapy gradually decreases serum sodium. Serum sodium should be assessed carefully, at least at 1 week after treatment. Some studies noted that there were no significant hyponatraemia associated with desmopressin use **(17)**. The incidence of hyponatraemia with desmopressin treatment ranges from 4.4% to 5.7% **(19)**. Moreover, Lower desmopressin dose and gender-specific dosing is of value to reduce clinically significant hyponatraemia **(20)**. As in one study there were reductions in serum sodium to <125 mmol/L in six women (taking >25mg desmopressin) and two men (aged 67 and 82 years) taking 100mg **(13)**.

These results are agree with **Chen et al.,(21)** assessed the serum sodium level at1,4,and12 weeks after initiation of desmopressin therapy. The mean (SD) decrease in the serum sodium levels was 3.89 (1.22) mmol/L (P<0.001) in the non-NP group and 4.69 (3.5) mmol/L (P<0.001)in the NP group.

In a study **Kim et al.,(17)** who investigated nocturia episodes in the voiding diary from the baseline to the final assessment in the desmopressin add-on group was significantly superior to that seen with placebo (-1.13 ± 0.92 135 vs. -0.68 ± 0.79, p = 0.034).

Yoshida et al., (22) revealed tamsulosin treatment for 8 weeks in LUTS/BPH patients with nocturnal frequency ≥2 times per day significantly improved nocturia in about 60% of the analyzed patients; nocturnal voiding frequency was decreased from 3.1 ± 1.0 to 1.7± 1.0, and NPI was decreased from 41.9 ± 11.0% to 33.8 ± 10.9%**.**

Also, our results agree with other studies which reported patients with BPH have being nocturia may be due to NP or decreased nocturnal bladder capacity and the frequencies of night voids decreased by 64.3% with desmopressin + tamsulosin compared to 44.6% with tamsulosin- only treatment **(19,20)**.

The current study showed no significant difference founded at before treatment regard total IPSS. **Mohammed and Al-Hakeem,(23)** showed no significant differences between α-blocker group, and oral desmopressin group in IPSS total score before treatments. 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). **Berges et al.,(18**) reported that desmopressin was effective for nocturia because nocturnal polyuria in men with LUTS/BPH and total IPSS was significantly decreased by desmopressin treatment, regardless of concomitant alpha-blocker use.

Our results revealed no significant difference in ICIQ-N between groups. A study of **Kim et al.,(17)** who reported ICIQ-N was significantly improved in the desmopressin add-on group compared to the placebo group**.**

In our study, Group A significantly associated with better improvement at all 4 domain of sleep scales more than Group B except in GTS scale 2 as there was no significant difference between groups regard this scale. **Kojima et al.,(24)** reported that alpha blocker treatment for 24 months reduced nighttime urine production in correlation with an increase in daytime urine production in BPH patients with nocturnal polyuria.

Also**, Berges et al.,(18**) reported that hours of undisturbed sleep also increased significantly versus baseline by 74 %. Consistent with the prolongation of the first sleep period, the four subscales of the LSEQ showed improvement in sleep during desmopressin treatment resulting in a significant improvement in QoS**.**

The number of patients who slept ≥4 h was increased from 6 % at baseline to 71 % after treatment. An increase in the duration of the first hours of sleep is important since SWS occurs during the first 3–4 h of sleep. Disruption of SWS, even without a reduction in total sleep quantity, leads to daytime fatigue and somnolence, and a reduction in cognitive ability and overall functioning **(25).**

Additionally, an open-label study in men with nocturia due to NP showed that, after 10–12 months, the mean number of nocturnal voids was reduced by 48–58 % from baseline and the mean duration of firsthours of sleep was increased by 80–83 % **(18)**.

Therefore, 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

ISSN:0975-3583,0976-2833 VOL12,ISSUE 05,2021

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 **(23)**

CONCLUSION:

Oral desmopressin added to α-blockers is well tolerated and beneficial for improving the IPSS and nocturnal symptoms. Desmopressin can be expected to possess adual activity when used as an add-on therapy beside α-blockers in reducing nocturia as well as other LUTS.

No Conflict of interest.

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