Desmopressin Efficacy in Treatment of Nocturic Women- A Single-Blind Placebo-Controlled Study

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ABSTRACT

Background: Nocturia is night waking for voiding, is a lower urinary tract problem of anxious symptom. nocturnal polyuria, diminished capacity of the bladder either nocturnal and/or global capacity, and sleep impairment are main pathophysiologic subtypes. fluid restriction mainly awhile before the bed time, anticholinergic therapy, diuretics and hormone replacement therapy are main preventive strategies.

Aim of Study: To determine the oral desmopressin efficacy and safety of in nocturia of women as a treatment.

Patients and methods: - Sixty-four women with18-80 years' age with nocturia (nocturia index score >1, more than two voids per night) were invited to attend our study. randomly assigned patients into: 32 women received different desmopressin doses (0.2, 0.4, or 0.6 mg) during dose-titration period(three-weeks), and the other 32 ones received single- blind placebo treatment for 6 or 8 weeks according to their response.

Results: In single-blind phase, for desmopressin, 30 (93.75 %) patients with fifty percent or more nocturnal voids reduction against the baseline levels in comparison to only 3 (9.7%)placebo-receiving patients where ($P < 0.001$). The mean nocturnal voids No., sleep period till 1st nocturnal void, nocturnal diuresis, and allover day volumes changed signscantly preferring desmopressin. ($P<0.001$).

Conclusions: women with nocturia better to be treated with oral desmopressin and informed about tolerance and effectiveness.

Keywords: Desmopressin efficacy; nocturic women; A single-blind placebo.

INTRODUCTION

Nocturia, defined as a night waking for voiding (Van Kerrebroeck and Weiss, 1999) is a problematic lower urinary tract symptom (LUTS) (Miller, 2000; Peter, 1997). The incidence is an age increasing with [Donahue and Lowenthal, 1997; Barker and Mitteness, 1998) incidence risen from (thirty to sixty percent) in a 49 yrs. mean aged population (60- 90%) in a population aged sixty to 80 years (Barker and Mitteness, 1998; Hale et al 1986), it is underdiagnosed LUT problem (Stewart et al., 1992) and also increase the old aged mortality (Asplund, 1999).

polyuria, decrease nocturnal capacity of bladder and/or global bladder capacity, and sleep impairment are the main pathophysiologic categories (Drake. 2012).

Night urine Overproduction of (nocturnal polyuria) is main cause of nocturia (Asplund,1995; Rembratt et al.,2001). Antidiuretic hormone secretion of (arginine vasopressin (AVP) might be decreased (Miller,2000; Drake. 2012). The fall in AVP secretion is age related (Miller,2000). Behavioral modification (fluid restriction) mainly awhile before the bed time, diuretics hormone replacement therapy, and anticholinergic therapy are the treatment approaches (Lose et al.,2001). Nocturnal polyuria is rarely to be reduced by fluid restriction because in recumbent position the interstitial fluid redistributed (Matthiesen et al.,1996). Diuretics had shown reduction in nocturia; but if taken before bedtime it exacerbates nocturia (Drake,2012). Therapy by Anticholinergic is of benefit, where bladder dysfunction consider as an underlying cause (Harbison, 2012).

Desmopressin (des-Amino-D-arginine vasopressin, DDAVP) acetate is a long acting synthetic analogue of AVP (antidiuretic hormone) its efficacy proved to in polyuria conditions, such as nocturnal enuresis (Hjalmas et al.,1998) and diabetes insipidus (Vilhardt ,1990). oral, sublingual Desmopressin acetate tablets is available. And also in form of nasal spray and injection (Bennett and Brown, 2008). The intranasal adult dose for (10-20) micrograms daily (Eckford et al.,1995). It is also the only peptide for which an oral formulation is currently available, albeit with a bioavailability of only 1% (Bennett and Brown, 2008). Tablets of DDAVP are prescribed initially at 0.2 –0. 6 mg daily mostly in single dose (Eckford et al.,1995). Where by mimicking the AVP action it is successfully used for the last 30 years, desmopressin acetate decreases urine production and increases urine osmolality (Eckford et al.,1995). The main side effect of desmopressin acetate is hyponatremia, which can have prevented by allowing short period some polyuria for the patient each week (Eckford et al.,1995), its side effects are hyponatremia, headache, facial flushing, nausea vomiting and rarely seizures (Eckford et al.,1995). Desmopressin acetate has many interactions with either individual drugs or with groups of drugslike: - Alpha antagonists, Beta blockers, Phosphodiesterase inhibitors, Tricyclic antidepressants, Anticholinergic mainly oxybutynin, Chlorpromazine, Carbamazepine (Seiler et al.,1992). Desmopressin has also been shown to cause asignificant decrease in nocturnal urinary volumes (Drake. 2012).

Aim of study

This study aimed to determine the Desmopressin tablets efficacy and safety in the nocturia women treatment.

PATIENTS AND METHODS

Study design

Randomized interventional blind trial (study).

Place of study

Consultancy clinic of Ghazi AL Hariri hospital at Medical City Complex in Baghdad was the place of study

Time of study

It was from first of October 2016 to the last week of September 2017.

Population of study

Women ≥18 years, who with nocturia attending consultancy clinic of Ghazi AL Hariri hospital were the study participants

Inclusion criteria

1. Woman aged 18 years and older.

2. Patient complained nocturia more than two voids per night.

3. Clients with nocturnal /24-hour voided urine ratio > 20% and 33% in adult and elderly respectively.

Women who fitted criteria of inclusion and with index score of nocturia > than 118. In the phase of dose- titration, the women were administered bedtime oral desmopressin of (0.2 mg) with in first week. where full treatment response by no nocturnal voids and it selected as optimum dose. Non response exposed to 0.4 mg during 2nd week. If fail dose would increase to 0.6 mg during week 3.

Exclusion criteria

Reasons for exclusion included: -Pregnancy, patients with urethritis or vaginitis, and patients with abnormal urine or blood in urine, Serum Na levels below normal range or at the lower limit of normal value, certain preexisting conditions (multiple sclerosis), diabetes insipidus, [>40 mL/kg per 24 hours]). Patients with overt LUT dysfunctions had been excluded, antihypertensive; except diuretics.

Sampling technique

Sample size was assumed to be statistically acceptable (32 for drug group and 32 for placebo group) after screening of 100 patients.

The patients were selected for screening by systematic randomization. In SRS- 1-10. Every third patient had inclusion criteria following the first number chosen; which resemble the patient; were selected in each consultancy day for the whole study period. Participants were verbally informed about the study aims. Based on their approval, participants were asked to sign the consent forms.

The sample size: was based on assuming that the patients treated with the drug will get response, if reduce no. of voiding by >50% at night as a primary end point, secondary end point resembling many factors like nocturnal void times, sleep period, nocturnal diuresis and 24- hour urine volume in milliliter.

Data collection

This study was applied two phases: (1 week) screening, and randomized single-blind treatment as a titration of dose (till three weeks) for patients receiving desmopressin continue to 3-5 weeks according to their response, and 8 weeks for patients received placebo. During the screening period age, body weight in kilograms, height in meter, number of voids per night, time of starting the sleeping, period from sleeping till waking to the first nocturnal void, urine volume in night and day, mean of nocturnal void per 24-hour voided urine, intake of fluid, and micturition frequency were recorded in 100 patients. After screening, nocturia diagnosis had been confirmed

Eligible patients were randomly assigned to receive either their optimum desmopressin dose or placebo.

Department of Pharmacy and Drugs Sciences in Baghdad Teaching Hospital/Medical City Complex approved the randomization lists and treatments were stratified by dose and center.

The study duration started from (6 weeks) for those achieving optimal response at the lowest dose to 8 weeks, Serum sodium measured; adverse events recorded, open squares.

Serum sodium was monitored once at screening, potentially three times during dose titration, and a final measurement at end of single-blind period. Patient would be withdrawn during the study if any of the following applied: serum sodium less than 125 mmol/L or symptomatic hyponatremia, failure to cooperate, experience of an intolerable adverse event.

Operational definition

The safety had been assessed to every patients taking even one dose of the medication.

The primary efficacy: the proportion of women with a ≥50% reduction in the nocturnal voids number as in comparison with baseline levels (clinically improved). Secondary end points: changes in the mean number of nocturnal voids, duration of the sleep period until the first nocturnal void, nocturnal diuresis and 24 hours' urine volumes. Further, abbreviated version of the Bristol female LUTS (BFLUTS) questionnaire was determine the impact on safety and quality of life. During screening period 36 were excluded on the basis of failing to accompany the inclusion criteria and have their reasons for exclusions. The sixty-four women who were admitted in our study and were subsequently randomly assigned into the single-blind treatment period they received either desmopressin (n = 32) at their optimum dose or placebo (n = 32). In total, 63 of 64 (98%) patients completed the study. The withdrawal was one in the Desmopressin group because of fatality. Patient

deposition is summarized in Fig 1.

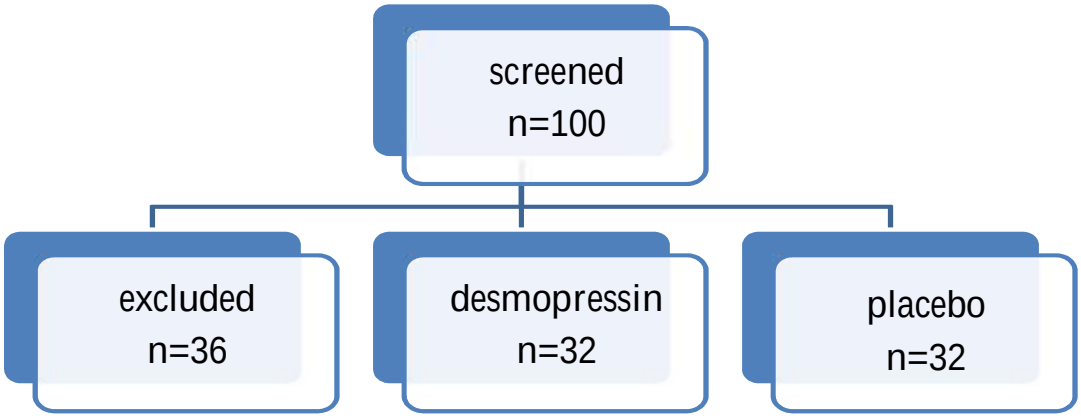

Figure 1: Patient distribution in the study.

As an indicator of acceptability and treatment tolerability, where, 60% completing the single-blind treatment period agreed to continue therapy in 10- or 12-month follow-up studies.

Reported laboratory measurements and adverse events were assessed for treatment safety evaluation.

Statistical analysis

Statistical analyses by SPSS version 17 by the Community Medicine Department in the College of Medicine/Baghdad University.

Study Ethics

Ethical approval was obtained from all participating women and special questions request form was applied and filled correctly and regularly.

RESULTS

The mean age was significant higher in1st (placebo) than in 2nd (desmopressin) group, (p <0.001), other Patients demography were similar for both ITT population groups table1.

Body mass index was of no significant difference between two groups of ITT patients, table 1.

Table 1: Distribution of age and BMI of studied sample (ITT)

Variable	Desmopressin	Placebo	Total	t-test	P
Age(years) Mean ± SD	52±3.8	58±5.2	64	5.27	< 0.001
BMI(kg/m²) Mean ± SD	27.1±6.1	26.9±5.8	64	0.13	0.89

Clinical improvement in the ITT population, was obtained in 30 (93.75%) patients receiving33 desmopressin 7compared with 5 (15.6%) receiving placebo (P < .001), table 2.

Table 2: Clinical improvement in both two groups of ITT patients

Improvements	Yes		No		Total	
	No.	%	No.	%	No.	%
Desmopressin	30	93.7	2	6.3	32	100.0
Placebo	5	15.6	27	84.4	32	100.0
Total	35	54.7	29	45.3	64	100.0

P= 0.0001 by Fishers exact test

The patients proportion of response is dependently on the dose, where, response rate in desmopressin 11group was statistically significant higher than in the other group (p<0.001), table 3 and figure 3.

Clinical response rates at 3rd week for patients treated with desmopressin and placebo were 62% and 0.3%, respectively. No response for treatment was observed among 6.5% of patients received desmopressin and among 90.3% of patients received placebo. All these finding were shown in table 3& figure 2.

Table 3: Clinical response rate among studied two groups.

Groups	1st week	2nd week	3rd week	No	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)

Desmopressin	2(6.5)	8(25.0)	20(62.0)	2(6.5)	32(100.0)
Placebo	2(6.5)	1(3.2)	0	29(90.6)	32(100.0)
Total	4(6.0)	9(14.0)	20(32.0)	31(48.0)	64(100.0)

$\chi^2 = 48.96, DF = 3, p < 0.001$

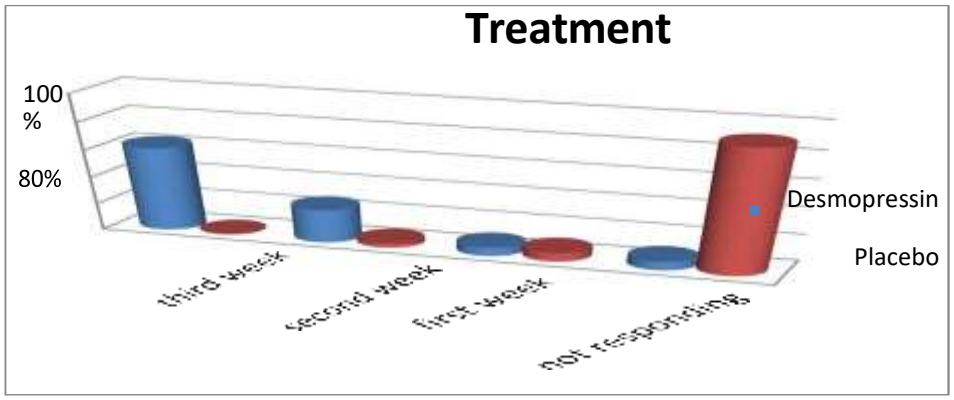

Figure 2: Distribution of the patients according to their response to treatment.

At the end of the single-blind treatment period, the mean number of nocturnal voids was almost halved from 3 to 1.5 in (75%) of the desmopressin-treated group compared with 3 to 2.5 voids per night in placebo group, but only (17%) got ≤1.5 void (p <0.001), table 4 and 7.

Table 4: Effect of treatment types on nocturnal voids of patients.

Mean number of nocturnal voids			Mean number of nocturnal voids		Total	
	>1.5		≤1.5			
	No.	%	No.	%	No.	%
Desmopressin	8	25.0	24	75.0	32	100.0
Placebo	26	83.0	6	17.0	32	100.0
Total	34	53.1	30	46.9	64	100.0

$\chi^2 = 20.33, DF = 4, p < 0.001$

The sleep duration mean till the 1st nocturnal void was prolonged by 2:10 hours to 6:32 hours in the desmopressin group compared with an increase of 2:17 to 3 hours from starting the sleeping time in the placebo group. The 98 minutes' difference between 2 groups is statistically significant (P < .001). 24 (75%) desmopressin patients had more than 180 minutes of undisturbed night period sleep, while only 4 (12.5%) in the placebo group (p <0.001), table 5 and 7.

Table 5: Effect of treatment types on sleep period of the patients.

	Mean duration of sleep period					
	> 180min		≤ 180min		Total	
	No.	%	No.	%	No.	%
Desmopressin	24	75.0	8	25.0	32	100.0
Placebo	4	12.5	28	87.5	32	100.0
Total	28	43.7	36	56.3	64	100.0

Fishers exact test, p<0.001

The mean N.D duration of the desmopressin group decreased by 0.7 ml/min while in the placebo group by about 0.1 ml/min, and there was a significant difference in the volume of urine between the two studied groups (p<0.001), table 6.

Regarding the mean of 24-hour urine volume, in the desm.111 group there was a reduction (5.7%) while in placebo (4.3%) (P<0.001), table 7.

Table 6 : Effect of treatment types on nocturnal diuresis of the patients.

Nocturnal diuresis	Desmopressin	Placebo	t-test	P
Mean ± SD ml/min	0.8±0.1	1.35±0.3	9.84	<0.001

Table 7: Values of secondary end point mean (SD) of Desmopressin, mean (SD) of Placebo

Variable	Baseline	Rx	% change*	Baseline	Treatment	% change*	Mean đ	P
Nocturnal Voids	3 (0.9)	1.5 (0.9)	-50.0	3 (0.9)	2.5 (0.3)	-16.0	-1	ş
Sleep period min.	130 (32)	272 (46)	+100.0	137 (31)	181 (33)	+32.0	+98	ş
Nocturnal Diuresis	1.5 (0.4)	0.8 (0.1)	-47.0	1.44 (0.4)	1.35 (0.3)	-7.0	-0.6	ş
24-hr urine Volume	1782 (75)	1680 (68)	-5.7	1762 (72)	1686 (71)	-4.3	-26	ş

*=percentage of end treatment values difference, đ= difference between placebo and desmopressin. as the mean values absolute change, ş = p< 00.001.

BFLUTS questionnaire analysis demonstrate that 2 groups were similar for urinary symptoms after this study, the nocturia prevalence fell from 100% to 6.3% in the desmopressin group compared with placebo group from 100% to 84.4%. others nocturia reduced from 97% to 12%, 98% to 84% in desmopressin, placebo group respectively. There were significant statistical improvements in bothersome of nocturia were shown for desmopressin treatment as that for placebo (p<0.001). Thus, perception of patient for quality of life improvement reflected forth efficacy.

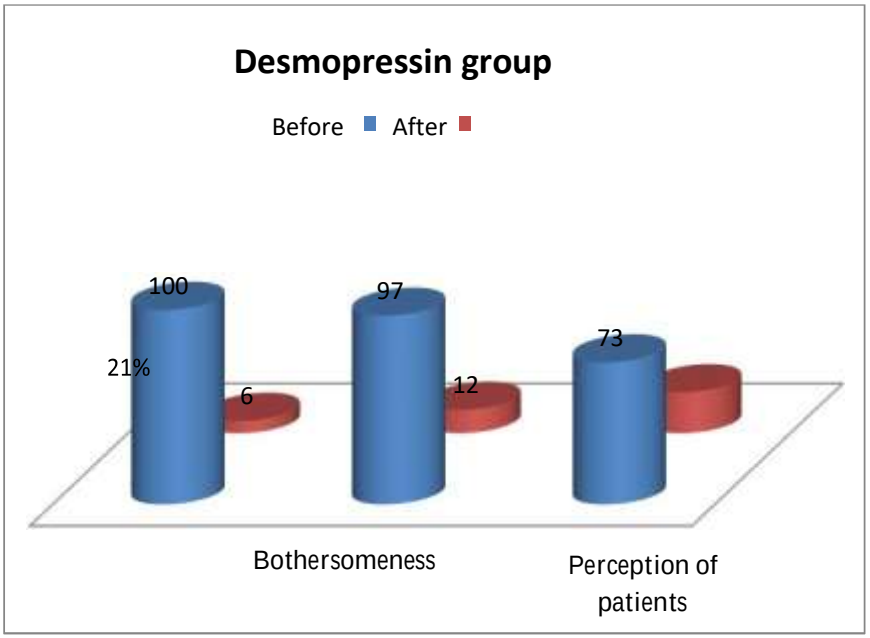

Figure 4: BFLUTS questionnaire symptoms before and after desmopressin treatment.

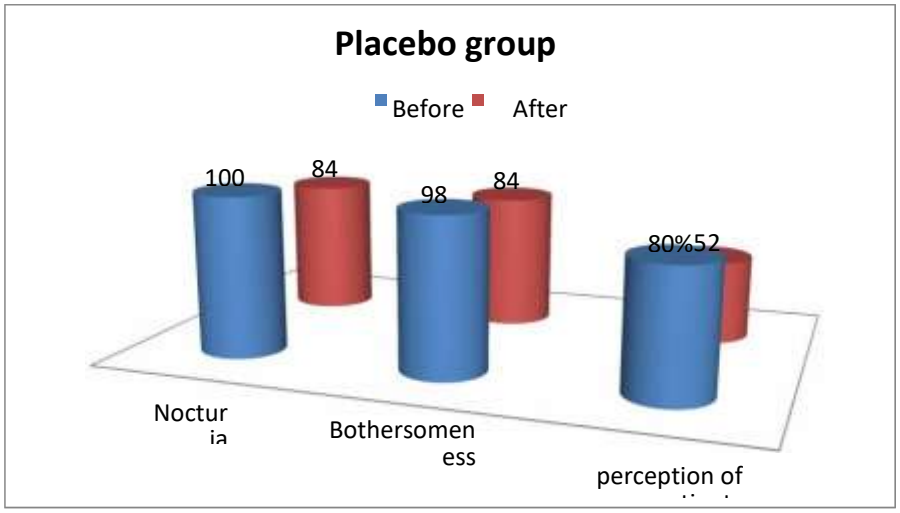

Figure 5: BFLUTS questionnaire symptoms before and after placebo treatment.

the frequency of adverse events patients was obviously high in Desmopressin treatment groups with 16 (50%) versus 6 (18.75%) in placebo groups, respectively. headache was the most frequent adverse event, which was reported in 8 (25%), 2 (6%) of desmopressin- and placebo respectively.

During the study, one (3%) patient had serious adverse event reported after completing the course of treatment a fatal outcome was recorded for her. All these findings were shown by table 8.

Table 8: Adverse events summary.

Single-blind The Events	Desmopressin No. (%)	Placebo (%)	No.
Patients enrolled	32	32	
Total side Events	16 (50.0)	6 (18.75)	
Serious side events	0	0	
Death *	1(3%)	0	
Adverse events related to study medication	16 (50.0)	6 (18.75)	
Headache	8 (25.0)	2 (6.0)	
Nausea	4 (12.0)	2 (6.0)	
Hyponatremia	1 (3.0)	0	
Peripheral Edema	3 (9.0)	2 (6.0)	

Regarding the fatality, however, the patient died subsequently of unrelated causes., the patient was complaining of onset of adverse events of gangrenous diabetic foot and that underlying diabetic complications was the fatal outcome.

DISCUSSION

Nocturia is passage of urine overnight, and many individuals will not regard nocturia on only one occasion per night as being of clinical significance (Asplund Aberg,1983).

Female patients with nocturia who responded to desmopressin (50% reduction of nocturnal voids) were treated effectively.

A desmopressin that is given orally leads to nocturnal voids reduction 93.75% of patients treated with desmopressin and their response rate was 62% at 3rd week of treatment, in other hand, 9.7% of placebo treated patients had reduction in nocturnal voids and 90.3% of them were not responding to treatment. The primary end point measures chosen were clinically relevant and it was consistent with findings of previous literature (Borbely et al.,1981).

A secondary E.P. showed nocturnal voids significant decrease in and prolongation of sleep period for desmopressin treated patients as compared with also desmopressin treatment appeared to constitute normalization to values within the physiological range (Asplund and Aberg,1996; Rembratt et al.,2003; Drake. 2012). determinant of the sleep not only, where quality of sleep had been assessed (Asplund and Aberg,1996) and well-being in middle age and elderly women (Rembratt et al.,2003), but is also related to increased mortality (Asplund,1999).

and risks of falling at night (Stewart et al.,1992) particularly in the elderly. the duration of sleep significantly prolonged by Desmopressin, until the first nocturnal void, which consider

as important life quality indicator (Lose et al.,2003). There was a significant difference in nocturnal diuresis between the 2 groups in the study. Patients with desmopressin treatment had a significant decrease in 24-hours urine volume as compared with patients with placebo. All these findings of secondary end point effectiveness are consistent with results of previous literatures (Kirkland et al.,1983; Drake. 2012).

The nocturnal voids mean number were minimized by 50% in desmopressin patients, were only 5% reduction in placebo. There were reductions in nocturnal and 24-hour urine volume in patients receiving desmopressin, drinking habits slight changes is the possible cause. anti- diuretic Treatment agent that increase the renal fluid recycling of by urine osmolality increasing leading to minimized urine production. low arginine- vasopressin people are of night feeling thirst, so by receiving this drug they do not get such feeling and fluid intake consequently is reduced at night.

the mean ratio decrease of urine output in in patients on desmopressin would had been more if they had been maintaining the same patterns of drinking so, the same volume for the 24-hour urine.

by 272 minutes, the duration of the period sleep had been prolonged by desmopressin till the first void the quality of sleep id determined by this initial period therefore the life quality is determined by such role (Lose et al.,2003).

For safety, study also show that side effect associated were usually infrequent and mild.

These was competent with the established safety profile when using desmopressin in the as a part of management of polyuria. Only 1 (3%) patient recorded low Na as an adverse event, in total, 4 (25%) patients recorded S, Na with normal range (lower limit). Three of these patients were characterized by serum sodium levels 130 mmol/L. All of them were 65 years' age or older. No recorded data withdrew due to hyponatremia during the dose-titration period. Also there were no reports of S. Na values below the normal range throughout the treatment period (single- blind) and this is consistent with results of other literature (Kirkland et al.,1983).

Further research into the pathophysiologic mechanisms underlying nocturia and its effect on sufferers are required and effective therapies including desmopressin are needed. nocturia in male, Desmopressin treatment of patients with has demonstrated similar results (Matthiesen et al.,1996), and a previous study showed that desmopressin was well tolerated by nocturia long- term treatment (Hjalmas et al.,1998).

CONCLUSION

Efficacy and safety (short-time) of desmopressin as a treatment strategy for nocturia in women had been proved where, pivotal results of desmopressin as a well-tolerated and effective treatment in nocturia women.

RECOMMENDATIONS

1. We suggest giving more interest and attention for women complaining of nocturia because we found it underdiagnosed, even it will disturb sleep patterns, and contribute to mortality increase.
2. We recommend the types of treatment according to the situations and response of the patients including modifications of behavior; such as fluids restrictions, anticholinergic treatment, diuretics, and hormonal replacement therapy.

CONFLICT OF INTEREST

Authors stated that there is no any kind of conflict of interest for this study.

FUNDING

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ETHICAL CLEARENCE

Ethical clearance was taken from the institutional committee for research approval.

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