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Original article:

The Efficacy And Safety Of Desmopressin In Patients With Benign Prostatic Hyperplasia With Persistent Bothersome Noctriuria

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ABSTRACT

Introduction: Noctriuria is the most common and usually the most bothersome lower urinary tract symptom (LUTS) of benign prostatic hyperplasia (BPH). Desmopressin has been shown to be beneficial in the treatment of noctriuria, however, studies evaluating Indian population are lacking. We aimed at evaluating the safety and efficacy of desmopressin in men with BPH and refractory noctriuria in the Indian population.

Material and methods: This prospective study evaluated men > 50 yrs of age with bothersome LUTS on alpha blockers with bothersome persistent noctriuria, defined as 2 or more voids nightly with or without nocturnal polyuria. All patients underwent standard urological investigations along with serum electrolyte measurement, international prostate symptom score (IPSS) calculation and 72hour voiding diary and were started on oral desmopressin 0.1mg HS for 6 weeks. At 6weeks, all patients were re-evaluated with 72hr voiding diary, IPSS, serum electrolytes, USG-PVR, and were assessed for relevant side effects. The number of episodes of noctriuria, change in serum sodium and IPSS at baseline and at 6 weeks were compared.

Results: A total of 30 men were included, mean age was 69.8 years. As compared to the baseline, the nocturnal voided volume post therapy reduced significantly (from 620 ml to 555ml) and there was a decline in the number of nocturnal voids by 0.6 voids/night (p=0.01). The serum sodium levels also reduced significantly, however, they remained within the normal range in all but 1 patient.

Conclusion : Desmopressin is safe and effective in men with bothersome persistent noctriuria due to BPH despite alpha blockade.

Keywords: Desmopressin; LUTS, Benign Prostatic Hyperplasia

INTRODUCTION

Voids that are preceded and followed by sleep are called as nocturnal voids and getting up two or more times to micturate is considered abnormal (1). Noctriuria is the most common and usually the most bothersome lower urinary tract symptom (LUTS), reported by 72% of elderly men (2,3). Besides being bothersome, nocturnal voids disturb sleep and result in daytime somnolence and increase the risk of falls and hip fracture, thus have a deeper impact (4,5). Noctriuria is multifactorial, the cause may be the bladder, either detrusor overactivity, small capacity of bladder or raised post void residual volumes or may be the kidneys, with increased urine production. Besides the urinary system, sleep disorders, sleep apnea, cardiovascular system and diabetes mellitus may also cause noctriuria. Benign prostatic hyperplasia (BPH) may cause bladder outlet obstruction and can result in bladder related issues and finally noctriuria (6). Sixty percent of men with BPH have detrusor overactivity which may result in noctriuria (7).

Raised post void residual volumes, because of incomplete voiding due to obstruction by enlarged prostate may reduce the functional bladder capacity which may inturn increase the number of nocturnal voids (6). Besides these, age related detrusor overactivity, and age related changes in bladder capacity may also play some part (7).

Another important cause is nocturnal polyuria, defined as nocturnal urine volume >20-33% of the total 24-hour urinary volume (8). Around 93% of all the elderly patients who report noctriuria demonstrate nocturnal polyuria (9). Whereas, increased nocturnal urine production (nocturnal polyuria) results from age related changes in serum levels of anti diuretic hormone (ADH) (10). Advancing age is also commonly associated with cardiac abnormalities. Reduced cardiac output leads to peripheral edema during the hours of erect posture (waking) and this excess fluids return to the heart during supine posture (night hours) and also contributes to nocturnal polyuria (5).

Bothersome LUTS due to BPH are initially treated by alpha blockers and anti-muscarinics but these symptoms may not resolve especially if nocturnal polyuria is the primary cause. Desmopressin, a synthetic analogue of ADH and binds to the V2 receptors in renal collecting ducts causing water reabsorption. When administered at bed time, it lowers nocturnal urine production and noctriuria. Desmopressin has been extensively evaluated for the treatment of noctriuria and nocturnal polyuria, however, studies evaluation Indian population are lacking. We aimed at evaluating the safety and efficacy of desmopressin in men with BPH and refractory noctriuria.

AIMS AND OBJECTIVES

Evaluation of safety and efficacy of desmopressin in men with BPH and refractory noctriuria.

MATERIAL AND METHODS

This prospective study was carried out at a tertiary care hospital from Jan 2018 to Nov 2018 after obtaining ethical clearance. Men > 50 yrs of age with bothersome lower urinary tract symptoms (LUTS) for >3months with an IPSS of 14 or more on alpha blockers (for voiding symptoms) with / without anticholinergics (for storage symptoms) for at least past 3 months, either at maximal dose or at maximally tolerated doses were screened. Of these, those who complaint of persistent bothersome noctriuria defined as 2 or more voids nightly with or without nocturnal polyuria (defined as nocturnal urine greater than 33% of total daily urine volume) were included in this study after informed consent. Patients with active urinary infection, clinically significant outflow obstruction (max flow rate <12ml/sec and or post void residual urine >100ml), urge incontinence, voiding dysfunction, on indwelling foley catheter or performing intermittent catheterisation or on condom catheter (unable to self void), chronic inflammatory conditions such as interstitial cystitis, bladder stones, current or previous malignancy of pelvic organs, past history of pelvic radiation, any current or recent cardiac, renal or liver disease, concomitant use of other drug treatment for incontinence / non drug treatment eg electrostimulation for incontinence or intravesical onabotulinum toxin use within the last 1 year or receiving treatment with drugs known to interact with desmopressin (eg diuretics, tri-cyclic antidepressants, indomethacin, carbamazepine or chlorpropramide) or suffering from any condition medical or surgical which in the opinion of the investigators make the use of anti-cholinergic contraindicated (as deemed by investigator) were excluded for this study. All patients underwent standard urological investigations such as body weight measurement, urine routine, culture, kidney function tests, serum electrolyte, uroflometry, ultrasonography KUB region with post void residual volume measurement, serum prostatic specific antigen estimation and international prostate symptom score (IPSS) calculation. All patients who consented for inclusion in the study were

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asked to make a 72hour voiding diary. After recording these baseline data, all patients were started on oral desmopressin 0.1mg HS. Patients we advised to micturate just before sleeping and not to drink fluids more than sufficient to satisfy thirst from 1 hour before bedtime until 8 hrs after the drug intake. They were advised to avoid drinking fluids and diuretics (caffein and tea) at night (after 8pm). All patients were reviewed at day 1, 1 week, 3 weeks and 6 weeks after initiation of drug treatment. At day 1 and 1 and 3 weeks follow up all patients were asked for any beneficial effects, relevant side effects such as constipation, dry mouth, confusion, nausea, vomiting, weight gain, headache, dizziness etc and serum sodium levels was evaluated. If serum Sodium levels fell more than 5mg% below the baseline or patients develop dizziness or confusion, the medication was discontinued and patients were treated as per advise of nephrologist with intra-venous salt replacement. At the last follow up at 6weeks, all patients were evaluated with body weight, 72hr voiding diary, IPSS, serum electrolytes, USG-PVR, and were assessed for relevant side effects such as constipation, dry mouth, confusion, nausea, vomiting, weight gain, headache, dizziness etc. and the medication was discontinued. The number of episodes of noctriuria, change in serum sodium and IPSS at baseline and at 6 weeks were compared using parametric and non-parametric tests and a p value <0.5 was considered significant.

RESULTS

A total of 30 patients were included. The mean age was 69.8 years (66-75 years). All patients were on alpha blockers for greater than 3 months, 16 of these were also taking antimuscarinics. The mean baseline IPSS was 21.0 (15-27), mean 24 hour voids were 9.1 (7-12), mean nocturnal voids were 3.2 (2-5), mean 24 hour voided volume was 2035.5ml (1650-2400ml), nocturnal voided volume was 620ml (400-800ml) and 10 of the 30 (33.3%) had nocturnal polyuria. The prostate volume was 36.5 gm (21-58gm) and the mean SPSA was 2.3 ng/ml (1.1-3.9 ng/ml). The mean Qmax was 17.2ml/sec (14-21ml/sec), the mea Qavg was 7.3ml/sec (5-10ml/sec) and the mean voided volume was 205ml (150-280ml). The mean baseline serum sodium was 140.1mEq/dL (137-145mEq/dL).

The 6 weeks post treatment findings and the comparison with baseline is presented in table 1. The nocturnal voided volume reduced significantly (from 620 ml to 555ml) and there was a significant decline in number in nocturnal voids also from a mean of 3.2 to 2.6 voids per night. The serum sodium levels also reduced significantly, however, they remained within the normal range in all but 1 patient, thus were statistically significant but clinically insignificant.

In only one patient the serum sodium fell below the cut off value, but the decline was not greater than 5mg%. None of the patients complained of nausea, vomiting, dizziness or confusion related to drug intake. None of the patients discontinued therapy due to adverse effects.

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Table 1 : comparison of various parameters at baseline and at 6 weeks post treatment

Parameter	Baseline	6weeks post treatment	P value
IPSS score	21.0 (15-27)	20.2 (16-25)	0.4
24 hr voided volume	2035 (1500-2450)	2061 (1700-2450)	0.6
Nocturnal voided volume	620 (400-800)	555 (300-750)	0.04
24 hr voids	9.1 (7-12)	8.6 (6-11)	0.2
Nocturnal voids	3.2 (2-5)	2.6 (1-5)	0.01
Number of men with nocturnal polyuria	10	9	0.7
Qmax	17.2 (14-21)	18 (10-21)	0.07
Qav	7.3 (5-10)	7.1 (4-10)	0.7
Voided volume	205 (150-280)	194 (165-235)	0.1
Serum Sodium	140 (137-145)	138 (132-145)	0.03

DISCUSSION

The current study evaluated the safety and efficacy of desmopressin in men with persistent bothersome noctriuria despite alpha blockers. With the addition of desmopressin for 6 weeks, the nocturnal voided volume reduced significantly (by 65ml) and the number of nocturnal voids reduced by 0.6 voids per night (p=0.01). The serum sodium also reduced significantly, however, it did not fall below the normal cut off range and thus this effect was clinically insignificant. None of the patients developed severe adverse effects or discontinued therapy. Thus, in this study, desmopressin was found to reduce number of nocturnal voids and the nocturnal voided volume, but the magnitude of reduction was small.

Alpha blockers are the usual first choice therapy in men suffering form noctriuria because of BPH (11). They reduce the number of nocturnal voids (by 0.8-0.9 voids/night) and improves the IPSS score (12). Besides alpha blockers, antimuscarinics as well as desmpressin has also been shown to improve noctriuria (12). Antimuscarinics reduce the number of noctriuria by 0.6-0.7 voids/night, however, this reduction did not reach statistical significance (12). Only when the patients with nocturnal polyuria were excluded, antimuscarinics were found to significantly reduce noctriuria (13). Thus antimuscarinis are best for men without nocturnal polyuria and also improve irritative LUTS such as urgency and urge incontinence.

Desmopressin, on the other hand, improves noctriuria in men with and without nocturnal polyuria (12). Desmopressin, as compared to a placebo, has been shown to significantly reduce the number of nocturnal voids by 0.87 times/night (12,14). Van Kerrebroeck et al, in their double blind placebo controlled study, evaluated 127 men with noctriuria and found a significant reduction in the number of nocturnal voids in the desmopressin arm (absolute difference of -0.84 in the desmopressin arm as compared to placebo). Also, 34% of patients on desmopressin recorded a >50% reduction in the number of noctriuria episodes as compared to 10% in the placebo arm (14). In the present study, the number of nocturnal voids reduced by 0.6 with around 10% recording a >50% reduction in the

number of voids. This reduction reached a statistically significant level, however, a reduction of such a small magnitude may not have clinical relevance.

Desmopressin has also been shown to reduce the nocturnal voided volume and increase the first sleep period (12,15). A study by Asplund et al, evaluating elderly men with nocturnal polyuria, found that desmopressin significantly reduced nocturnal diuresis by 0.59ml/min compared to those on placebo (15). This reduction in nocturnal diuresis was dependent on the baseline level of night time dieresis. The day time urine production was unaltered. All these beneficial effects were reversed on discontinuation of therapy (15). We also found a significant improvement in nocturnal voided volume by 65ml and did not note any alterations in day time voided volume with the use of desmopressin in the present study. Also, desmopressin has been shown to improve the first sleep period by 59% as compared to 21% in the placebo arm. We did not evaluate the first sleep period, by a reduction in nocturnal dieresis the first sleep period may have been increased in our study as well. Also, we did not note any night time falls during the study period.

One of the major limitations of desmopressin use especially in elderly men is its effect on serum sodium. Desmopressin, by retaining water, causes dilutional hyponatremia (12). Hyponatremia has been occasionally noted in various studies evaluation desmopressin in elderly men, even when all these studies included only men with normal baseline serum sodium levels (12). Hyponatremia has been reported in 3-4% of the study population on desmopressin in the literature (12,14). In the current study, only one patient developed hyponatremia at 6 weeks, that too was >130mEq/dL and thus did not require treatment other than discontinuation of therapy. No major untoward drug related events were recorded in the present study.

CONCLUSION

Desmopressin is safe and effective in men with bothersome persistent noctriuria due to BPH despite alpha blockade. The magnitude of clinical effect, however, is small and there is a risk of hyponatremia. Thus, the clinicians need to assess the risk benefit ratio before prescribing desmopressin.

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