

DESMOPRESSIN ORAL LYOPHILISATE LESSENS THE BURDEN OF NOCTURIA IN THE POST-TURP MEN SOONER THEY GO ASLEEP – AN ACTION UNREACHABLE BY FLUID RESTRICTION ALONE BUT ATTENUATED BY AGING

Hypothesis / aims of study: Desmopressin oral lyophilisate (“DRUG”), known for its reliable bioavailability and fast action in handling water in renal tubules(1), may shed light on treating persistent nocturia in men following TURP for LUTS/AUR, for which effective treatment is in lack(2). A RCT is conducted to (A) compare (i) the dynamic action of “DRUG” { variation of the average hourly urine excretion rate (“UER”) across the bedtime period } with placebo in post-TURP men; (ii) the reduction of the hourly “UER” by “DRUG” (“ ΔUER_{DRUG} ”) between young ($\leq 70y.o.$) and old ($>70y.o.$) men; (iii) the time elapsed between retiring to bed and 1st nocturia (“1stNtime”) before and after the treatment “Tx” & between placebo and “DRUG” & (B) determine the cut-off value of post intervention “1stNtime” (“TIME”) with which to characterize subjective improvement of the nocturia and satisfaction with “Tx” by the men.

Study design, materials and methods: A prospective, randomized, double blind, placebo-controlled trial (RCT) is carried out to study the action & clinical efficacy of “DRUG” in treating post-TURP men bothered by persistent nocturia (≥ 2 per night by diary). 47 post-TURP men {mean age(y.o): 69.5, range 57-75; $\leq 70y.o.$ (N=24); $>70y.o.$ (N=23); weight(kg): 66.7, range 47-86; Qmax (ml/sec, SD): 15.8 ± 7.9 ; voided volume (ml, SD): 294 ± 149 ; PVR (ml,SD): 60 ± 48.5 } were recruited. 45 men had nocturnal polyuria. They were then randomized to receive either “DRUG” 60 μ g (N=22) or placebo sublingually (N=25) 60 min before bedtime nightly for 4 weeks. They had to empty their bladders before sleep and thoroughly fill out a voiding diary for 4 consecutive days before & in the last 4 days of “Tx”. The average hourly “UER” was derived from “{volume of voided urine divided by time elapsed between 2 voidings (ml/hour)}”; and the values of UER for each hour spanning across the voiding diaries (pre-Tx & post-Tx) were determined. “ ΔUER ” was defined as: - { “ ΔUER_{DRUG} ” = [UER_{post-Tx} - UER_{pre-Tx}]_{DRUG}; “ $\Delta UER_{placebo}$ ” = [UER_{post-Tx} - UER_{pre-Tx}]_{placebo} }. The hourly “ ΔUER_{DRUG} ” across bedtime was compared between men $\leq 70y.o.$ (N=9) and $>70y.o.$ (N=13) receiving “DRUG” and to their respective placebo groups (“ $\Delta UER_{placebo}$ ”). Subjective perception of the outcome (improvement of nocturia and satisfaction with “Tx”) was documented. “1stNtime” of placebo gp was compared to that of “DRUG” gp; ROC curve analysis was done to determine “TIME”. Serum Na were checked at screening, day 3,7,21. Statistical significance is denoted p <0.05.

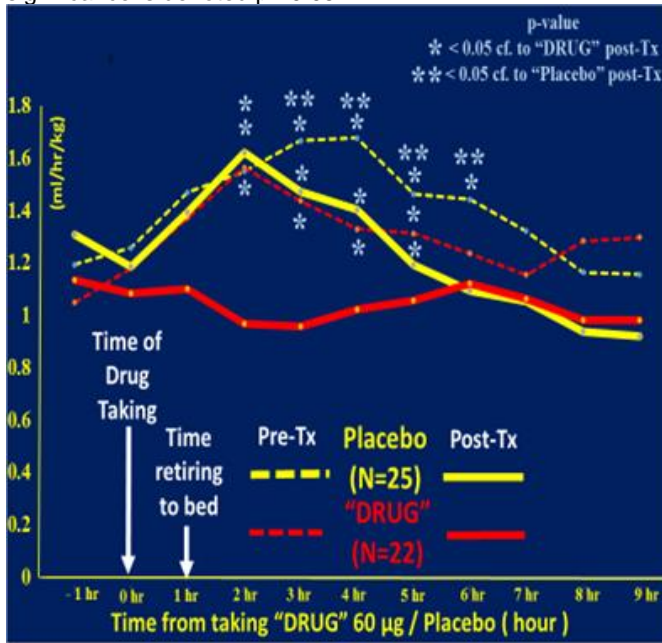


Fig 1. Variation of the Average Hourly “UER” per Body Weight (ml/hr/kg) with respect to the Time from Taking “DRUG” 60 μ g / Placebo

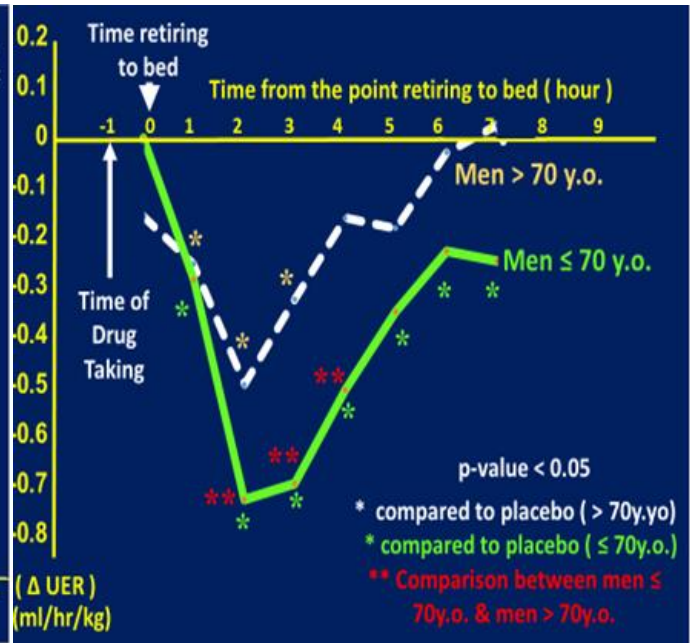


Fig2. (“ ΔUER_{DRUG} ”) per body weight (ml/hr/kg) with respect to Time from Retiring to Bed between men $\leq 70y.o.$ and $>70y.o.$

Results: Dynamic profile of “UER” across bedtime of both “Tx” gps and that of “ ΔUER_{DRUG} ” between men $\leq 70y.o.$ & $>70y.o.$ was shown in Fig 1&2 respectively. Nocturia was lessened in “DRUG” gp ($\downarrow 37\%$) as compared to placebo gp ($\downarrow 15\%$) (p=0.038) in men $\leq 70y.o.$ but not in men $>70y.o.$ ROC analysis showed that “TIME”=185 min (AUC=0.701, p=0.018) and 211 min (AUC=0.676, p=0.051) are to regard the “Tx” as being able to improve nocturia (185min) and “Tx” result as being satisfactory (211min), respectively. Other results are tabulated in table 1.

Table 1. Comparison between Placebo group and “DRUG” group for parameters derived from the voiding diary

	Placebo (N=25)			"DRUG" (N=22)				
Table 1	Pre-Tx	Post-Tx	statistical significance within group (p-value)	Pre-Tx	Post-Tx	statistical significance within group (p-value)	p-value between groups (pre-Tx)	p-value between groups (post-Tx)
DIURNAL urine output per body weight per 24 hours (ml/kg) +/- (SEM)	18.199 +/- 2.156	16.947 +/- 2.139	0.28	18.125 +/- 1.333	17.381 +/- 1.429	0.474	0.977	0.871
NOCTURNAL urine output per body weight per 24 hours (ml/kg)(+/-SEM)	12.364 +/- 1.199	10.427 +/- 0.962	0.002	11.781 +/- 0.787	8.745 +/- 0.934	<0.001	0.695	0.22
TOTAL urine output per body weight per 24 hours (ml/kg +/- SEM)	30.564 +/- 3.149	27.374 +/- 2.882	0.022	29.906 +/- 1.774	26.131 +/- 1.883	<0.001	0.862	0.727
No. of DIURNAL micturition per 24 hours (+/-SEM)	7.003 +/- 0.336	6.51 +/- 0.428	0.149	7.136 +/- 0.586	6.886 +/- 0.397	0.614	0.84	0.526
No. of NOCTURNIA per night (+/- SEM)	2.593 +/- 0.143	2.081 +/- 0.211	0.017	2.852 +/- 0.215	1.955 +/- 0.221	<0.001	0.311	0.682
Average DIURNAL bladder capacity per micturition (per body weight) (ml/kg) (+/-SEM)	2.549 +/- 0.227	2.507 +/- 0.234	0.745	2.738 +/- 0.229	2.611 +/- 0.205	0.069	0.563	0.746
Average NOCTURNAL bladder capacity per micturition (per body weight) (ml/kg) (+/-SEM)	3.449 +/- 0.299	3.446 +/- 0.282	0.982	3.218 +/- 0.241	3.039 +/- 0.256	0.244	0.557	0.295
RATIO: Average NOCTURNAL bladder capacity / Average DIURNAL bladder capacity (+/- SEM)	1.431 +/- 0.102	1.409 +/- 0.063	0.832	1.228 +/- 0.066	1.207 +/- 0.081	0.762	0.113	0.0495
Average Volume of 1st NOCTURIA per body weight (ml/kg) (+/-SEM)	3.641 +/- 0.389	3.991 +/- 0.374	0.196	3.417 +/- 0.332	3.239 +/- 0.323	0.441	0.669	0.141
RATIO: 1st NOCTURIA volume of urine to urine volume produced during bedtime (+/-SEM)	0.301 +/- 0.021	0.425 +/- 0.041	0.005	0.291 +/- 0.021	0.421 +/- 0.047	0.002	0.744	0.944
Time elapsed between retiring to bed to 1st NOCTURIA (min) (+/- SEM)	148.001 +/- 11.345	164.187 +/- 15.214	0.264	140.379 +/- 11.332	229.001 +/- 21.532	<0.001	0.638	0.016
TOTAL BEDTIME (min) (+/- SEM)	479.213 +/- 11.046	473.627 +/- 10.072	0.618	502.758 +/- 17.015	497.985 +/- 15.196	0.654	0.241	0.179
RATIO: time to 1st NOCTURIA / TOTAL bedtime duration (+/- SEM)	0.312 +/- 0.024	0.356 +/- 0.036	0.179	0.281 +/- 0.022	0.465 +/- 0.044	<0.001	0.346	0.049
Average Urine Excretion Rate for 1st NOCTURIA (ml/kg/hour) (+/- SEM)	1.681 +/- 0.234	1.6718 +/- 0.188	0.856	1.562 +/- 0.169	0.973 +/- 0.125	<0.001	0.651	0.004

Interpretation of results: No hyponatremia was noted. Placebo & “DRUG” did NOT change the diurnal/nocturnal bladder capacity, diurnal micturitions, volume of 1st nocturia and total bedtime (Table 1). In contrast, both groups of men had readily reduced their daily fluid intake after the recruitment to similar extent by ~11-12% (N.B. reduced daily total urine output). Following that were the significant and similar reduction of nocturnal urine output and number of nocturia in both groups **after “Tx”** (Table 1). However, only men receiving “DRUG” could remarkably extend “1stntime” (from 140 to 229 min) associated with the drastic decrease in UER, (“ΔUER”_{DRUG} %~↓45%) (Fig 1 & 2) in the early hours of sleep, peaking at ~3 hours after drug administration. This observation failed to be replicated just by restricting fluid intake alone, whereby the “1stntime” was barely increased by 16 min (Table 1) yet the much wanted “decreased nocturnal urine production” merely appeared in the latter hours in bed (placebo group Fig. 1) from which older adults(>60y.o) are less able to get deep & restorative sleep (3). This notable pharmacodynamics of “DRUG” will give clinical benefit provided that “1stntime” can be prolonged to at least 3 –3.5 hours (“TIME”) after the men have retired to bed. Of note, this action profile (“ΔUER”_{DRUG}) is less pronounced in men >70y.o., being of lower magnitude (40% less), shorter duration of action (~3 hrs shorter) (Fig 2) & uncertain reduction in nocturia.

Concluding message:- Desmopressin Oral Lyophilisate lessens the burden of nocturia by remarkably prolonging the time to first nocturia in post-TURP men mainly via its action profile in the early phase of the sleep but this profile tends to diminish with age.

References

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Disclosures

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