

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

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Introduction & Aims of study : Desmopressin Oral Lyophilisate (“**DRUG**”) possesses reliable bioavailability and fast action in handling water in renal tubules in young people (1). Persistent nocturia in men following TURP for LUTS / AUR is common but short of effective treatment (2). This study explored the action & clinical efficacy of “**DRUG**” in treating post-TURP nocturia by:-

(A) Comparing

- (i) Its dynamic action { variation of the average hourly urine excretion rate (“**UER**”) across the bedtime period } with placebo
- (ii) the reduction of the hourly “**UER**” by “**DRUG**” (“**ΔUER**”_{DRUG}) between young (≤ 70y.o.) and old (> 70y.o.) post-TURP men;
- (iii) the time elapsed (a) between retiring to bed and 1st nocturia (“**1stNtime**”) before and after the treatment (“**Tx**”) & (b) between placebo and “**DRUG**”

(B) Determining

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: Prospective, Randomized, Double Blind, Placebo-controlled trial (RCT)

Materials and Methods :

Subjects: Post-TURP men (N=47) with persistent nocturia (≥ 3 months & ≥ 2 per night by voiding diary) ; Nocturnal Polyuria: N=45 ; { Age of subjects (y.o.): mean=69.5, range 57-75; ≤70y.o.(N=24); >70y.o.(N=23) Weight of subjects (kg): mean=66.7, range 47-86 ; Peak micturition flow {Qmax} (ml/sec) : mean=15.8, SD 7.9; Voided volume (ml): mean=294, SD 149; Post-void residual {PVR}(ml): mean=60, SD 48.5 }

Intervention: “**DRUG**” 60µg (N=22) vs **Placebo** (N=25) (sublingually 60 min before bedtime nightly for 4 weeks)

Data collection: Voiding diary x 4 consecutive days before “**Tx**” & in the last 4 days of “**Tx**” and questionnaire for global impression of “**Tx**”.

Variables derived from voiding diary: Average hourly “**UER**” (ml/hour) = {volume of voided urine divided by time elapsed between 2 voidings } spanning across the bedtime (pre-Tx & post-Tx)

hourly “ΔUER”_{DRUG} = [UER_{post-Tx} - UER_{pre-Tx}]_{DRUG} across bedtime

hourly “ΔUER”_{placebo} = [UER_{post-Tx} - UER_{pre-Tx}]_{placebo} across bedtime

Outcome:

Comparison of “**ΔUER**”_{DRUG ≤70y.o.} (N=9) VS “**ΔUER**”_{DRUG >70y.o.} (N=13)
 “**ΔUER**”_{DRUG ≤70y.o.} (N=9) VS “**ΔUER**”_{placebo ≤70y.o.} (N=15)
 “**ΔUER**”_{DRUG >70y.o.} (N=13) VS “**ΔUER**”_{placebo >70y.o.} (N=10)
 “**1stNtime**”_{DRUG} VS “**1stNtime**”_{placebo}

Subjective perception of the outcome (improvement of nocturia and satisfaction with “**Tx**”) ; “**TIME**”

Statistical tests: paired t test / t test (parametric data); Wilcoxon rank sum test (non-parametric data) ; chi-square test (categorical data) ; ROC curve analysis for “**TIME**” ; p value denoted < 0.05

Results : Nocturia was lessened in “**DRUG**” gp (↓ 37%) as compared to placebo gp (↓ 15%) (p = 0.038) in men ≤ 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 (185 min) and “**Tx**” result as being satisfactory (211 min), respectively. Other results are tabulated in table 1.

Interpretation of result :

Both groups of men had readily reduced their daily fluid intake after the recruitment by ~11-12% associated with significant and similar reduction of nocturnal urine output and nocturnal episodes after “**Tx**” (Table 1). However, only men receiving “**DRUG**” could remarkably extend “**1stNtime**” (from 140 to 229 min) associated with the drastic ↓ UER, (“**ΔUER**”_{DRUG} % ~ ↓ 45 %) (Fig 1 & 2) in the early hours of sleep. This observation failed to be replicated just by restricting fluid intake alone, whereby the much wanted “decreased nocturnal urine production” merely appeared in the latter hours in bed (placebo group Fig. 1) in which older adults (> 60y.o.) are less able to get deep & restorative sleep (3). Patients will perceive clinical benefits provided that “**1stNtime**” can be prolonged to at least 3 – 3.5 hours (“**TIME**”). Of note, this action profile (“**ΔUER**”_{DRUG}) is less pronounced in men > 70 y.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.

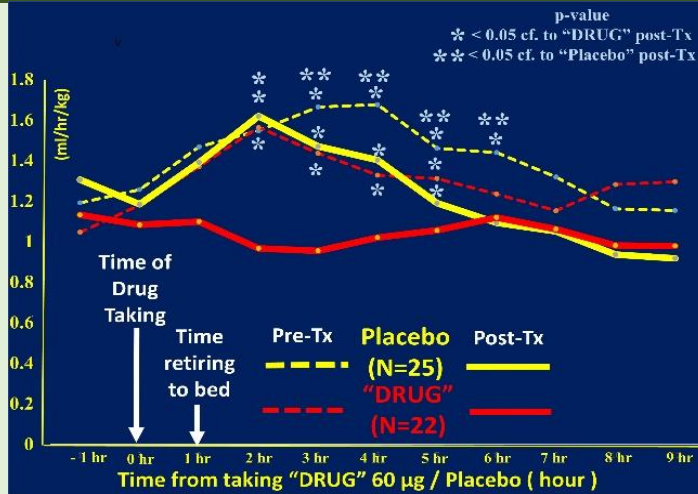


Fig 1. Variation of the Average Hourly “UER” per body weight (ml/hr/kg) with respect to the Time from Taking “DRUG” 60 µg / Placebo

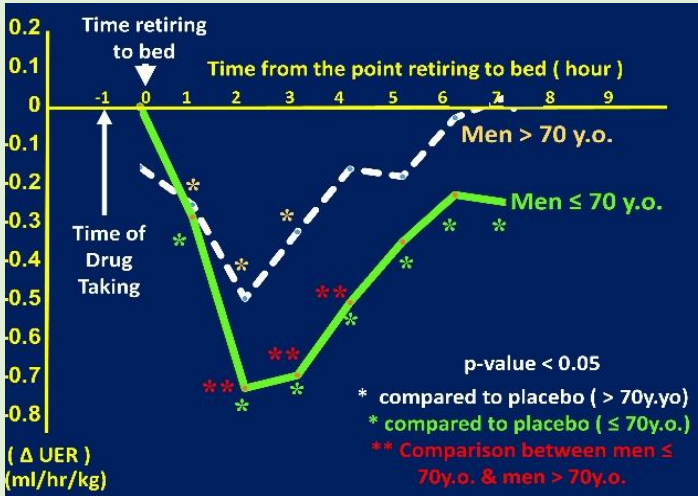


Fig 2. (“ΔUER”_{DRUG}) per body weight (ml/hr/kg) with respect to Time from Retiring to Bed between men ≤70y.o. and >70y.o.

Comparison between Placebo gp and “DRUG” gp for parameters derived from voiding diary

Table 1.	Placebo (N=25)			“DRUG” (N=22)			p-value between groups (pre-Tx)	p-value between groups (post-Tx)
	Pre-Tx	Post-Tx	statistical significance within group (p-value)	Pre-Tx	Post-Tx	statistical significance within group (p-value)		
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 NOCTURIA 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

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