

Efficacy of Tadalafil once daily versus Fesoterodine in the treatment of overactive bladder in older patients

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Abstract. – OBJECTIVE: Several studies have suggested that phosphodiesterase type 5 inhibitors (5-PDEi) show a potential therapeutic use in the treatment of overactive bladder (OAB) and male lower urinary tract symptoms (LUTS). The aim of this study was to evaluating the efficacy on OAB symptoms, impact on quality of life and sexual function of tadalafil 5mg once daily in older patients versus fesoterodine 8 mg.

PATIENTS AND METHODS: 108 consecutive patients diagnosed with OAB were divided into 2 groups: Group A: 56 patients treated with tadalafil 5 mg once daily; Group B: 52 patients treated with fesoterodine 8 mg, both groups treated for a period of 12 weeks. Eligible patients were men aged ≥ 65 years with OAB symptoms, including urgency and increased frequency during a period of ≥ 1 year and urgency urinary incontinence during a period of ≥ 6 months before enrolment. Patients were asked to complete the 3-day voiding diary prior each scheduled visit at weeks 0, 4 and 12. During these visits, they were administered: Overactive Bladder Symptom Score (OABSS), International Prostate Symptoms Score (IPSS), International Index of Erectile Function (IIEF-5) and Quality of life (QoL).

RESULTS: Not statistically significant differences emerged between the two groups at baseline, both patient groups had similar age and BMI; in each treatment group, the proportion of men ≥ 75 years was approximately 65%. From the results of our study, we can say that a treatment once a day with tadalafil improves not only significantly: micturition/24 hours ($p < 0.001$), urgency episodes/24 hours ($p < 0.003$), and urge incontinence episodes ($p < 0.001$) compared to fesoterodine treatment, but also the quality of life ($p < 0.001$) and sexual function ($p < 0.001$) in older patients.

CONCLUSIONS: These analyses demonstrate that tadalafil 5 mg once daily vs. fesoterodine 8 mg is efficacious in the treatment of the symptoms of OAB in older adults, improving also the quality of life and sexual and social life.

Key Words:

Overactive bladder, Antimuscarinics, Older patients, Sexual function, Phosphodiesterase type 5 inhibitors, Quality of life.

Introduction

The overactive bladder (OAB) syndrome by definition implies urinary urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia, in the absence of pathological or metabolic disorders (bladder outlet, known neurological conditions, urinary tract infection) that might otherwise cause such symptoms¹. It is a particular burden in older people, not only because of its higher prevalence (15% of people aged ≥ 65 years and 30-40% of people aged ≥ 75 years) but also because the impact of its symptoms may be more pronounced due to the increased burden of chronic comorbidities^{2,3}. Symptoms of OAB can disrupt patients' daily lives and occupation, and have significant negative impact on sleep quality and sexual function⁴. Antimuscarinics have demonstrated clinical efficacy for treatment of OAB symptoms and nocturia⁵; they are first-line medications for treatment of OAB⁶. The focus of therapy tried to reduce muscle activity (inhibiting muscarinic receptors) interacting through different peripheral and central signalling molecules⁷. Fesoterodine is the most recent addition to the class of muscarinic receptor antagonists and its efficacy has also been documented in many controlled studies^{8,9} and dedicated studies in elderly people¹⁰. However, older patients are known to experience more adverse events than younger patients, such as dry mouth and constipation¹¹.

Phosphodiesterase inhibitors (PDEi) prevent the degradation of cyclic guanosine monophos-

phate (cGMP) and cyclic adenosine monophosphate (cAMP), which are important mediators in maintaining smooth muscle tone. PDEi were originally designed to treat cardiovascular disease and were later used for the treatment of erectile dysfunction¹². There are 11 members in the family of PDEi characterized of which phosphodiesterase type 5 inhibitors (5-PDEi) (localized to penile and bladder tissue) have been shown to have potential therapeutic use in the treatment of OAB and male LUTS (Lower urinary tract symptoms)¹³.

The purpose of this study was to assess the efficacy on OAB symptoms, impact on quality of life and sexual function of tadalafil 5 mg once daily in older patients versus fesoterodine 8 mg.

Materials and Methods

In this prospective randomized study from December 2011 to February 2014, 108 consecutive patients diagnosed with OAB were treated as it follows: Group A (GA) consisted of 56 patients treated with tadalafil 5 mg once daily for a period of 12 weeks; Group B (GB) counted 52 patients treated with fesoterodine 8 mg once daily for a period of 12 weeks. During treatment period each patient was randomized 1:1 tadalafil or fesoterodine.

All study participants provided written informed consent prior to enrolment. Eligible patients were men aged ≥ 65 years with OAB symptoms, including urgency and increased frequency during a period of ≥ 1 year and urgency urinary incontinence during a period of ≥ 6 months before enrolment. Exclusion criteria included: urinary retention from benign prostatic hyperplasia, urethral stricture, bladder neck contracture, postvoid residual urine volume (PVR) > 80 mL, underlying neurological disease responsible for OAB, active urinary tract infection, interstitial cystitis, bladder stone, history of pelvic malignancy or pelvic radiation, bladder urinary tract surgery. Patients taking medications with antimuscarinic were also excluded. All patients were instructed on how to fill in the voiding diary. Patients were asked to complete the 3-day voiding diary prior each scheduled visit at weeks 0, 4 and 12. During these visits, they were administered: Overactive Bladder Symptom Score (OABSS), International Prostate Symptoms Score (IPSS), International Index of Erectile Function (IIEF-5) and Quality of life (QoL). Safety and tolerability were also evaluated within the study protocol, including the nature, frequency, and in-

tensity of adverse events, and withdrawals due to adverse events.

Statistical Analysis

All statistical analyses were conducted on Microsoft Excel 2010 platform. Statistical analysis of the mean values of continuous variables was performed using the Student's *t*-test and analysis of the significance of the categorical variables was performed using the chi-square and Fisher tests. A $p < 0.05$ was considered to indicate statistical significance.

Results

Three patients of GA dropped out of the study because of drug intolerance (headache and flushing), while two patients of GB abandoned the study, one for acute retention of urine which required urinary catheter placement and the other for dry mouth and constipation. Patients characteristics at inclusion are reported in Table I. Not statistically significant differences emerged between the two groups at baseline; both patient groups had similar age and BMI. The mean age of patients in the two groups was respectively: 71.2 ± 5.3 in GA and 72.1 ± 6.4 in GB; in each treatment group, the proportion of men ≥ 75 years was approximately 65%. The mean prostate volume was respectively: 42.35 ± 7.82 mL and 43.65 ± 6.72 mL;

The most common present comorbidities were hypertension 37.8% (39/103), diabetes mellitus 18.4% (19/103), heart disease 16.5% (17/103) and depression 10.6% (11/103). There was no significant difference in terms of OABSS (GA: 9.51 ± 2.37 ; GB: 9.87 ± 2.68), IPSS (GA: 17.39 ± 6.12 ; GB: 18.06 ± 7.02), IIEF-5 (GA: 13.4 ± 4.2 ; GB: 12.9 ± 3.1), QoL (GA: 4.94 ± 1.03 ; GB: 5.02 ± 1.35) at baseline in both groups (Table II).

However, at baseline in GA was observed a significant increase of nocturia compared to GB: 3.34 ± 1.02 vs 2.13 ± 0.68 respectively ($p < 0.001$), while in GB was observed a significant increase of urgency episodes/24 hours compared to GA: 4.53 ± 0.91 vs 3.32 ± 0.43 respectively ($p < 0.001$).

Therefore, analysis results indicate that in patients treated for 12 weeks with tadalafil (GA), have significantly improved compared to GB in IPSS: 11.27 ± 5.43 vs. 13.42 ± 4.75 respectively ($p < 0.003$), IIEF-5: 16.3 ± 5.5 vs. 14.12 ± 3.81 respectively ($p < 0.001$), and QoL: 3.18 ± 1.33 vs. 4.13 ± 1.22 respectively ($p < 0.001$).

Table I. Characteristics of the patients in the study.

Patients Characteristics	Tadalafil 5 mg (n=53)	Fesoterodine 8 mg (n=50)	p-value
Age patients (yrs) (mean):	71.2 ± 5.3	72.1 ± 6.4	NS
Number of patients (n) (%):			NS
≥65 years	18 (34)	16 (32)	
≥75 years	35 (66)	34 (68)	
Prostate volume (mL) (mean):	42.35 ± 7.82	43.65 ± 6.72	NS
Body mass index (kgm-2) (%):			NS
<18.5-24.9	14 (26.5)	18 (36)	
25.0-29.9	17 (32.0)	13 (26)	
>30.0	22 (41.5)	19 (38)	
Race (n) (%):			NS
White	53 (100)	50 (100)	
Other	0 (0)	0 (0)	
Mean duration of OAB (months)	48.4	50.1	NS
PVR (mL) (mean):	34.2 ± 19.7	37.5 ± 21.4	NS
Comorbidity (n) (%):			NS
Hypertension	21 (39.6)	18 (36)	
Diabetes mellitus	11 (20.7)	8 (16)	
Heart disease	7 (13.2)	10 (20)	
Depression	6 (11.3)	5 (10)	

NS: not significant; PVR: postvoid residual urine volume.

There were improvements in all four symptoms including frequency, nocturia, urgency episodes, and urge incontinence episodes in both groups; on the contrary, their correlations with OABSS have improved not significantly ($p < 0.204$). This improvement was progressive, both at weeks 4 and 12 (Table II).

Discussion

OAB is common and has a multifactorial pathophysiology, implying that it is difficult to conceive that one drug or drug principle would

be effective (enough) in all patients with OAB symptoms. Irwin et al¹⁴, studying 19,165 adult men and women, found that the prevalence in both men and women around 12% and that it increases with age. Therefore, OAB is a particular problem in older patients and this study shows that these patients tended to have greater levels of depression, anxiety, difficulties with social life, sexual relationships and a lower QoL¹⁵. Oral antimuscarinic agents are currently the mainstay of pharmacotherapy for treatment of OAB symptoms (frequency, nocturia, urgency micturition, and urge incontinence), but not for sexual disorders often related to them¹⁶.

Table II. OABSS, IPSS, main variables from 3-day voiding diary, QoL, and IIEF-5 score at baseline and weeks 4 and 12.

Parameters (mean)	Tadalafil			Fesoterodine			p-value
	Baseline	Week 4	Week 12	Baseline	Week 4	Week 12	
OABSS	9.51 ± 2.37	7.65 ± 2.77	5.97 ± 3.07	9.87 ± 2.68	8.14 ± 3.12	6.02 ± 3.59	<0.204
Micturition/24hours	12.77 ± 4.37	11.86 ± 3.97	9.22 ± 3.24	11.92 ± 4.68	11.03 ± 4.14	10.82 ± 3.86	<0.001
Urgency episodes/24hours	3.32 ± 0.43	2.89 ± 0.79	2.27 ± 1.5	4.53 ± 0.91	3.79 ± 1.12	3.54 ± 1.23	<0.003
Urge incontinence episodes/24 hours	1.67 ± 1.57	1.13 ± 1.10	0.52 ± 1.13	1.73 ± 1.32	1.56 ± 1.33	1.02 ± 1.37	<0.001
Nocturia	3.34 ± 1.02	3.06 ± 0.94	2.93 ± 0.89	2.13 ± 0.68	2.16 ± 0.87	1.79 ± 0.77	<0.005
IPSS	17.39 ± 6.12	14.63 ± 5.89	11.27 ± 5.43	18.06 ± 7.02	16.58 ± 5.35	13.42 ± 4.75	<0.003
IIEF-5	13.4 ± 4.25	14.47 ± 3.52	16.3 ± 5.56	12.9 ± 3.13	13.74 ± 3.52	14.12 ± 3.81	<0.001
QoL	4.94 ± 1.03	3.79 ± 0.98	3.18 ± 1.33	5.02 ± 1.35	4.67 ± 1.53	4.13 ± 1.22	<0.001

Fesoterodine is a relatively recent addition to the armamentarium of antimuscarinics for treatment of OAB. Pivotal clinical trials conducted in European countries and the United States^{17,18} have consistently shown both fesoterodine 4mg and 8mg once daily to be well tolerated and superior to placebo for improving OAB symptoms and bladder related problems. However, this antimuscarinic is associated with burdensome adverse events, such as dry mouth and constipation¹¹ that in our case were very important and responsible for the abandonment of the study for two patients.

Recently 5-PDEi have been shown to have potential therapeutic use in the treatment of OAB and male LUTS^{12,13,19}. These 5-PDEi (sildenafil, tadalafil and vardenafil) improve urinary symptoms in men with erectile dysfunction and OAB, and this finding has been confirmed in several well-designed randomized controlled trials^{20,21}. A single oral dose of tadalafil can exert significant positive effects on urodynamic parameters in patients with neurogenic bladder dysfunction associated with suprasacral spinal cord injury²². Morelli et al²³ suggest that in addition to relaxation of bladder muscle, PDE5 inhibition can increase blood perfusion of the bladder, causing an inhibitory effect on the non-voiding contractions during the filling phase.

We have observed that a treatment once a day with tadalafil improves not only significantly: micturition/24 hours: 9.22 ± 3.24 ($p < 0.001$), urgency episodes/24 hours: 2.27 ± 1.15 ($p < 0.003$), and urge incontinence episodes: 0.52 ± 1.13 ($p < 0.001$) compared to treatment with fesoterodine (10.82 ± 3.86 ; 3.54 ± 1.23 ; 1.02 ± 1.37 , respectively), but also the quality of life ($p < 0.001$) and sexual function ($p < 0.001$). Several studies have analyzed the functional impact of OAB on sexual life, participants with OAB reported anxieties related to sex linked to their body image and/or fears of incontinence^{24,25}.

However, in the group of patients treated with fesoterodine we have showed a significant improvement of the nocturia compared with GA ($p < 0.005$), although most likely the result may be distorted by a greater representation of random nocturia in patients in the GA at baseline.

This study concerned older patients with OAB eligible only for medical treatment and the median follow-up time of 12 weeks turned out to be insufficient. Thus, further studies with a longer follow-up are necessary. Moreover, other researches with more detailed exposure measure-

ment are warranted to evaluate questions about dose, the best age to begin the treatment and therapy duration. Randomized clinical trials will be essential to establish the efficacy and the safety of the best treatment regimen.

Conclusions

Unlike other previous studies, the focus of this work was to emphasize also the psychological impact of OAB on sexual life in older patients. These analyses demonstrate that tadalafil 5 mg once daily vs. fesoterodine 8mg is efficacious in the treatment of the symptoms of OAB in older adults, improving also the quality of life and sexual and social life. The lack of age-related differences in the tolerability of tadalafil simplifies management for the treating physician. Hence, tadalafil may be a more suitable first line option than antimuscarinics for the treatment of symptoms of OAB in older patients.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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