

THERAPEUTIC EFFECT CONSOLIDATION IN OVERACTIVE BLADDER TREATMENT IN ELDERLY WOMEN BY THE USE OF INCREASED ANTIMUSCARINIC DOSAGES

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Previously, the authors had carried out the study, in which the patients after trospium hydrochloride course with minimal or unstable therapeutic effect were administered the combination of trospium and an increased dosage of one of three antimuscarinics — oxybutinin, solifenacin and tolterodine for 6 weeks. This combination of drug therapy of elderly women with overactive bladder (OAB) was found to result in stable clinical and urodynamic result causing no additional side effects.

The present study was aimed at searching an optimal supporting course, which would enable to consolidate an initial effect and reduce the risk of OAB recurrence.

The aim of the investigation was to assess the possibilities of improving the supporting therapy efficiency in elderly women with overactive bladder using double doses of trospium hydrochloride and solifenacin.

Materials and Methods. The study included 229 women (mean age — 66.3 years: from 65 to 77) with clinically confirmed overactive bladder, who received daily trospium — 60 mg and solifenacin — 40 mg for 6 weeks (such treatment regimen had been justified in the previous study). In order to study the possibilities of each type of supporting therapy, the patients were divided into four groups: group 1 (n=59) was given trospium (60 mg o.d.) + solifenacin (40 mg o.d.) for a month; group 2 (n=51) — detrusor electrical stimulation for a month; group 3 (n=63) — laseropuncture for a month; and group 4 (n=56) patients were given placebo. A supporting therapy course followed the main course 2.5 months later. The patients' condition was monitored using OAB-q questionnaires (for a year) and urodynamic examination (before a treatment course, 6 and 12 months after the study initiation).

Results. A group of elderly women with OAB underwent a short course of treatment by high (double) doses of two antimuscarinics of different generations (trospium and solifenacin) 2.5 months after the main therapy, which had been similar, and enabled to maintain the initial clinical and urodynamic result for a long period of time (minimum 7 months), with the level of side effects being acceptable. The patients were found to have a high correlation of urodynamic and clinical indices on 6 and 12 month of the study. The use of detrusor electrical stimulation and laseropuncture as a supporting therapy does not enable to maintain a positive effect of drug therapy for a long time.

Conclusion. The supporting course of OAB treatment in elderly women by a combination of high doses of antimuscarinics two months after the main therapy course is the most effective method to reduce the symptomatic relapse risk of the disease.

Key words: overactive bladder; antimuscarinics; lower urinary tract dysfunction.

The prevalence of overactive bladder (OAB) increases considerably in women over 45–50 years. A third of women over 65 are found to have various lower urinary tract (LUT) impairments, and in the two thirds of these women OAB is accompanied by urinary incontinence that worsens their quality of life [1–3]. The development of overactive bladder in elderly women is explained by the decrease of functional competence of intramural ganglia and conducting afferent structures of detrusor, urothelial M₁- and M₄-receptors, by

generation of peculiar “afferent noise” resulting from chemo- and mechanoreceptors of urinary bladder membrane [4–6], muscular weakening of pelvic floor and pelvic organs; however, currently, some aspects of pathophysiological mechanisms of the process still remain debatable and need further elaboration [7–11].

OAB management by antimuscarinics is thoroughly studied [12–14]. Among anticholinergic drugs there are those having the highest level of clinical practice guidelines

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and evidences of efficiency: oxybutinin, solifenacin, tolterodine and trospium. However, the administration of these drugs in some patients falls short of expectations due to insignificant therapeutic effect [15–21]. In the previous studies (2008–2010) we succeeded in increasing therapeutic effect in elderly patients when used simultaneously two antimuscarinics and increased (doubled) dosage without enhancement of side effects that enabled to verify the results obtained by other research teams with other antimuscarinics selected, other spectrum of side effects studied and other treatment schedule [22–24].

However, the problem to maintain a stable result of OAB drug treatment in elderly women in a follow up period requires further investigation [25–27].

The aim of the investigation was to assess the possibilities of improving the supporting therapy efficiency in elderly women with overactive bladder using double-dosed trospium hydrochloride and solifenacin.

Materials and Methods. The study represents the second stage of clinical trials of OAB treatment efficiency in elderly women by combined high-dosed antimuscarinics. During the initial study (the first stage) 81 patients (mean age — 67.9 years; from 65 to 79) after trospium hydrochloride course with minimal or unstable therapeutic effect underwent a high-dosed combination therapy by trospium and one of three antimuscarinics — oxybutinin, solifenacin and tolterodine for 6 weeks. This combination of OAB drug treatment in elderly patients was found to result in a stable clinical and urodynamic results without increased side-effects. The best therapeutic effect was observed in a group of patients taking trospium, 60 mg, and solifenacin, 40 mg, daily (i.e. the doses were doubled compared to a manufacturer’s recommendations). Statistically significant differences between the groups were distinguished not for all urodynamic markers, but on the whole, in this group there was a clearer tendency towards normal values. A control study 4 months after the treatment revealed statistically insignificant worsening, 8 months later — statistically significant aggravation of the condition in most instrumental and clinical parameters.

In this study we focused on the search of optimal supportive course, which enables to consolidate an initial treatment effect and delay OAB recurrence maximally.

In many cases, OAB pathogenesis in men is known to be influenced by benign prostatic hyperplasia requiring an immediate treatment, and sometimes — surgery [28, 29]. Taking into consideration these factors, in the present investigation we brought into focus the study of optimal supportive OAB therapy for elderly women.

Within 2008–2010 we randomized 229 women (mean age 66.3; from 65 to 77 years) with urodynamic impairments and clinically confirmed OAB. All examined women received the most effective treatment schedule according to initial examination data (trospium 60 mg + solifenacin 40 mg, o.d., for 6 weeks), the result being similar to that at the first stage, and were divided into four groups according to a supporting therapy type: group 1 (n=59) — trospium (60 mg, o.d.) + solifenacin (40 mg, o.d.) for a month; group 2 (n=51) — detrusor electrical stimulation: an active electrode (50–70 cm²) — above the pubis, and a passive electrode (150 cm²) — in lumbosacral area, diadynamic current, frequency — 20 Hz, modulation depth — 50–75%, intensity — 20–40 mA, exposure — 15 min, a course consisting of 15 procedures every other day [30–34]; group 3 (n=63) — laserpuncture by helium-neon laser (632.8 nm) at acupuncture points RP 6, RP 9, VC 2 within 1–1.5 min for each point every day, light guide output power — 2 mW, 25 procedures [35–38]; group 4 (n=56) — placebo. The patients underwent a supportive course 2.5 months after the main therapy.

The patients’ state was monitored using questionnaires OAB-q [39, 40] (for a year) and an urodynamic examination (when grouping the patients, 6 and 12 months after the first course starting). The condition of lower urinary tract urodynamics was assessed in accordance with the guidelines of International Continence Society (ICS) [41, 42]. For urodynamic examination we used urodynamic system Relief-01 (DALPRIBOR, Vladivostok, Russia) with a double catheter, microtic (UROBAR, Germany). We studied the following parameters: bladder capacity at first desire to urinate (volume reflex) expressed in ml; bladder capacity at urinary urgency in ml; maximal pressure in detrusor (elasticity of detrusor) in ml/cm H₂O.

Initial data were acquired using an application Excel program of Microsoft XP and analyzed using JMP SAS

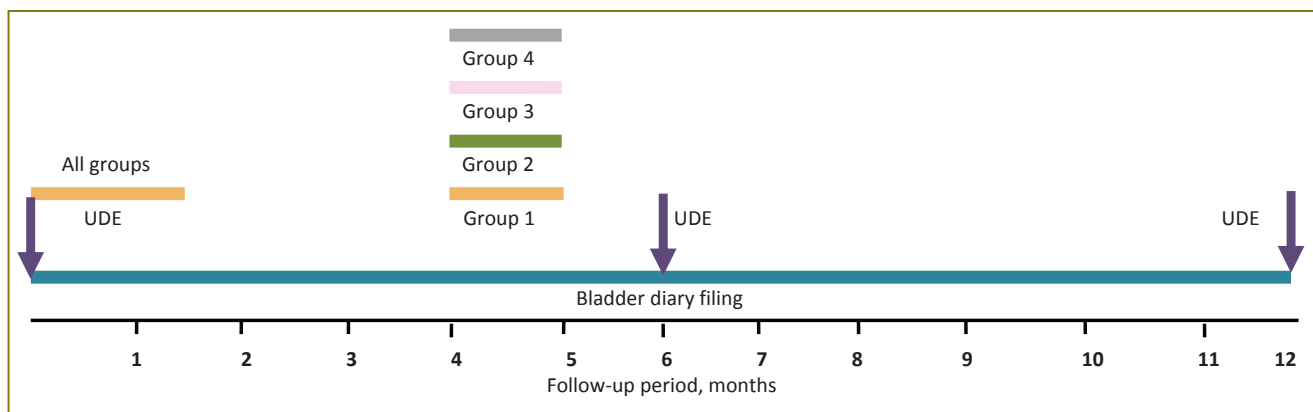


Fig. 1. Follow-up algorithm in elderly female patients with OAB (n=229). An arrow indicates urodynamic examination (UDE); an orange line — solifenacin (40 mg) and trospium (60 mg) intake, a green line — electric stimulation, a pink line — laserpuncture, a grey line — placebo intake

Statistical Discovery 8.0.2 (SAS Institute, USA). Wilcoxon and Kruskal–Wallis tests were applied to compare the findings in the groups before and after a supporting therapy course. We used analysis of variance (ANOVAs) and Tukey–Cramer test to compare the effects in the groups. P-values of <0.05 were considered statistically significant.

The study was carried out in accordance with Clinical Practice Guidelines [43, 44] and Helsinki declaration (adopted in June, 1964 (Helsinki, Finland) and revised in October, 2000 (Edinburg, Scotland)). Written informed consent was obtained from every patient before the examination.

Figure 1 shows the study design and treatment schedule.

Results. The more effective supportive therapy was observed in group 1 (See the Table and Fig. 2). An average

number of incontinence episodes (NIE) decreased within the first month of the therapy and continued decreasing up to 1.1 (0.7) episodes 6 months later ($p < 0.01$) remaining stably low after a year (1.5 (0.9); $p < 0.05$). Group 1 had a high correlation of urodynamic and clinical indices ($R = 0.6$; $p < 0.05$, when comparing NIE and bladder capacity samplings at first desire to urinate). Bladder capacity at first desire to urinate statistically significantly differed from initial (145.8 (37.6) ml), both in the first control study after 6 months (289.3 (63.7) ml; $p < 0.01$), and in the definitive study after 12 months (257.5 (28.9) ml; $p < 0.01$). Maximum capacity level had the same tendency of statistically significant increase in both control studies (313.7 (47.1) ml; $p < 0.01$ and 279.9 (33.8) ml; $p < 0.05$; initial level — 180.1 (31.0) ml). Elasticity of detrusor (20.2 (2.5) ml/cm H₂O) increased by one third by the sixth month of the study and

Urodynamic examination data and progress notes in groups (n=229)

Groups	Diary data (±SD)						Urodynamic indices (±SD)					
	Number of urinary incontinence episodes a day			Volume at the first desire to urinate, ml			Volume at maximal desire to urinate, ml			Maximum pressure in urinary bladder, ml/cm H ₂ O		
	before treatment	6 months after the treatment	12 months after the treatment	before treatment	6 months after the treatment	12 months after the treatment	before treatment	6 months after the treatment	12 months after the treatment	before treatment	6 months after the treatment	12 months after the treatment
Group 1 (n=59)	4.9 (1.5)	1.1 (0.7)**	1.5 (0.9)*	145.8 (37.6)	289.3 (63.7)**	257.5 (28.9)**	180.1 (31.0)	313.7 (47.1)**	279.9 (33.8)*	20.2 (2.5)	32.8 (6.0)*	28.8 (4.7)*
Group 2 (n=51)	5.3 (1.6)	2.2 (0.9)*	3.7 (1.3)	136.1 (37.7)	297.0 (45.3)**	210.9 (28.7)*	171.1 (45.0)	334.8 (38.3)**	251.9 (42.9)	17.5 (3.3)	35.4 (9.3)*	30.9 (4.9)*
Group 3 (n=63)	5.7 (2.5)	3.8 (0.8)	5.5 (1.4)	131.2 (54.5)	254.5 (49.1)*	199.3 (49.4)	168.3 (55.8)	286.0 (36.6)*	178.9 (29.0)	21.3 (6.6)	38.9 (7.8)*	29.8 (6.3)
Group 4 (n=56)	5.1 (2.1)	2.7 (1.1)	4.8 (2.4)	167.6 (32.1)	279.7* (54.8)	192.9 (28.9)	191.5 (58.6)	311.5 (51.7)*	206.3	21.9 (5.4)	31.0 (7.9)	23.9 (5.4)

Note: SD — standard deviation; * — $p < 0.05$; ** — $p < 0.001$; “before treatment” — indices before initial therapy.

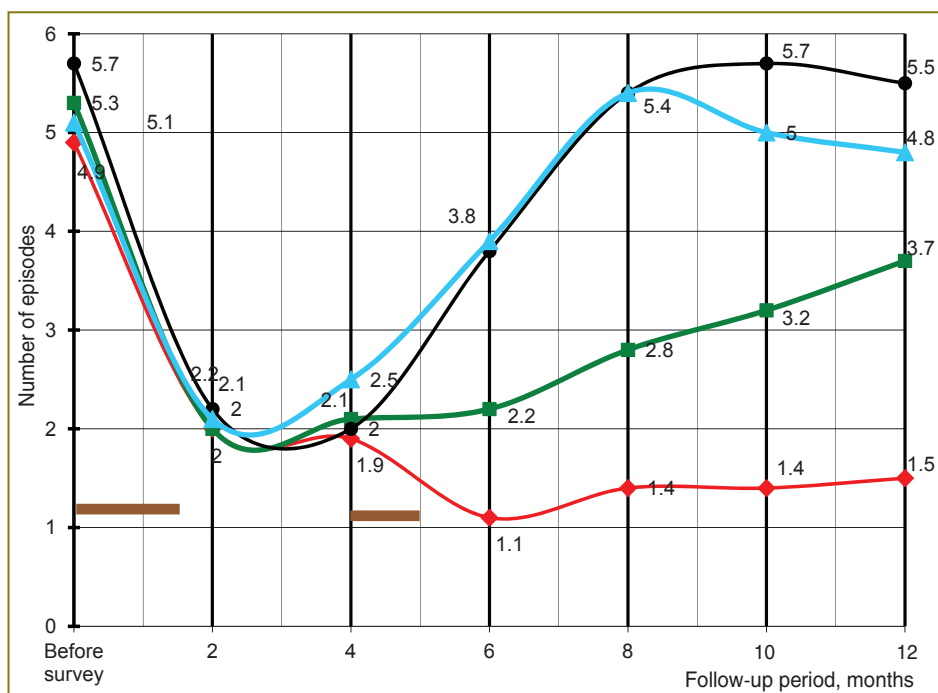


Fig. 2. Frequency of urinary incontinence episodes in elderly female patients with OAB (n=229): — group 1 (n=59); — group 2 (n=51); — group 3 (n=63); — group 4 (n=56). Horizontal lines indicate the time of the main therapy course and the supportive treatment

remained stably high on study completion (32.8 (6.0) and 28.8 (4.7) ml/cm H₂O, $p < 0.05$ in both cases).

Groups 2 and 3 were observed to have satisfactory results of NIE in the supportive therapy after 6 months (2.2 (0.9) — for group 2, and 3.8 (0.8) — for group 3), with high correlation with urodynamic indices, but even by the 8th month the indices returned to their initial level in group 3 — 5.4 (1.2), and significantly increased in group 2 — 2.8 (0.9); $p \geq 0.05$. The total result for the groups appeared to be unsatisfactory. In group 2 NIE was 3.7 (1.3) — the differences with the initial level being statistically insignificant, though positive changes in volume parameters at the first desire to urinate and detrusor elasticity still differed from initial, $p < 0.05$. In group 3 urodynamic indices at the end of the survey did not statistically significantly differ from initial ones.

In group 4 (placebo group) NIE returned to its initial level by the 8th month of the study, and final urodynamic findings did not differ from initial either.

Within a one-year follow-up period there was one lethal case related to acute heart failure outside an active therapy phase; 19 of 229 female patients (8.3%) discontinued the treatment and monitoring: in 14 patients due to side effects — intolerable xerostomia (9), headaches, vertigo (3), meteorism (1), nausea, vomiting (1); in 3 cases the treatment was discontinued at an early stage at patients' request due to the lack of an immediate positive effect; and in 2 cases — for the reasons unrelated to the treatment course. Thus, at final stage (1 year after the beginning of the examination) urodynamic examination was carried out and diary notes were analyzed in 208 female patients (90.8%).

Discussion. We have found that a short OAB treatment course in elderly women by high-dosed two antimuscarinics of different generations, which have an effect mainly on different muscarinic receptors, 2.5 months after the main course, and similar to it, enables to succeed in maintaining an initial clinical and urodynamic result for a long period of time. The application of bladder electrical stimulation as relay treatment turned out to be less effective — though NIE level remained lower at control study compared to an initial one, it did not statistically significantly differ from that; urodynamic indices worsened as well, but on the whole, urinary bladder volume at the first desire to urinate and detrusor elasticity appeared to be statistically significantly different from initial ones. In laseropuncture and placebo groups, urodynamic examination and the study of clinical OAB manifestations revealed the results to worsen even by the 6–8th months prompting suggestions that laseropuncture is ineffective as supportive treatment modality in elderly women with OAB.

The results obtained in group 1, from our point of view, illustrate well not only the efficiency of the combined effect of different antimuscarinic agents on suburothelial M₂- and M₃-receptors, which, as a rule, preserve quite well in urinary bladder of elderly women, but also a high stability level of functional activity of receptor apparatus in a supportive therapy course. Synergic activation of various receptors and, probably, the effect of stimulated M₂- and M₃-receptor on different structural levels of the detrusor, if trospium

and solifenacin are given to elderly women repeatedly, can be one of rational explanations of positive results of the suggested therapy course [4–6]. The attempt to have an effect on detrusor microcirculation using electrical stimulation appears to be unconvincing due to short-term effects, and, apparently, due to the lack of specific effect of receptors, predominantly preserving in the urinary bladder of elderly women.

Conclusion. The study has proved the earlier data on high efficiency and safety of combined treatment of OAB in elderly women by high-dosed trospium and solifenacin, and enabled to state that the repetition of a similar course of therapy after 2–3 months statistically significantly reduces OAB recurrence within a year, if the level of side effects is acceptable. The application of such physiotherapeutic methods as electrical stimulation and laseropuncture does not enable to continue a positive effect of drug therapy for a year. A supportive OAB therapy in elderly women by a combination of high-dosed antimuscarinics is the most effective way to reduce the incidence of recurrent disease.

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