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Elderly Men with Overactive Bladder: Maintenance of Satisfactory Therapeutic Effect of Administration of Combined High-Dosed Antimuscarinics

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ABSTRACT

Objectives: The performance management of the long-term results of treatment of overactive bladder (OAB) in elderly men.

Patients and Methods: The focus of the study was a search for an optimal maintenance regimen that would secure the initial effect of treatment with double doses of antimuscarinics and decrease the risk of the recurrence of OAB. One hundred and ninety-seven men (average age 68.7 years, from 65 to 77 years of age), suffering from urodynamically and clinically confirmed OAB, were included in this study. All examined patients received the most effective treatment regimen according to the data of the initial study (60 mg trospium and 40 mg solifenacin daily for 6 weeks) with a positive result, and then were distributed into 4 groups based on the type of maintenance therapy. Group A (49 persons): trospium (60 mg daily) and solifenacin (40 mg daily) during 1 month. Group B (41 persons): electrical stimulation of the detrusor during 1 month. Group C (43 persons): laser puncture during 1 month. Group D (48 persons): placebo. The cycle of maintenance therapy was conducted in 2.5 months after primary treatment had been completed. The monitoring of patient conditions was performed through the OAB-q questionnaire (during 1 year) and urodynamic examination (sixth and twelfth month from the beginning of the study).

Results: A monthly course of treatment with 2 high doses of trospium and solifenacin, conducted in Group A in 2.5 months after a main cycle with similar content, enabled the maintenance of the initial clinical and urodynamic results for a long period of time (no less than 7 months). The average number of daily incontinence events decreased after an initial cycle of antimuscarinics from 5.2 (1.3) to 1.3 (0.4) and remained consistently low in the sixth month, 1.5 (0.5), the ninth month, 1.5 (0.5), and twelfth month, 1.9 (1.1), differing from the initial level, with $P < 0.05$. Indices reflex volume, bladder capacity, and detrusor compliance showed improvements after the first cycle; after the second cycle of antimuscarinics these indices remained stable during all periods of monitoring.

Conclusion: An additional cycle of treatment with a combination of high-dosed trospium and solifenacin, conducted 2 months after the primary treatment, significantly decreased the probability of recurring OAB in elderly men during 1 year, with low-level side effects.

KEYWORDS:Overactive bladder, elderly men, antimuscarinic, physiotherapy

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INTRODUCTION

Overactive bladder (OAB) in elderly men is a common abnormality affecting quality of life. At least 40.4% of men over 65 years report constant or occasional symptoms of neurogenic urinal bladder [1-4].

Most researchers agree about the significance of the disorder of afferent innervation in the pathogenic mechanism of neurogenic dysfunction in the urinal bladder. Studies of pathology of ascending innervation specify 2 main links forming adequate or excessive signals. It is the urothelial functional block, consisting of the urothelium, interstitial cells, and afferent nerve fibers. Initial level of activation is represented by mechanoreceptors and chemoreceptors of mucosa. Second, myogenic activation is represented by mechanoreceptors of the muscle membrane of bladder generating signals at the contractive activity of myocytes. The central nervous system receives excessive information from the bladder, which is generated by different receptors providing "afferent noise" effects [5-7].

An issue concerning proper management of OAB symptoms is still the focus of many articles. Antimuscarinic agents, which proved themselves to be effective, still remain the first-line pharmacological treatment of OAB because of the rapid positive effect and small quantity of side effects [8-10]. But their long-term effects are often unstable and result in a comparatively rapid recurrence of pathological signs [11,12]. Due to this, research of potential efficiency, safety, and the stability of the effects of recent drugs, such as mirabegron and onabotulinumtoxin A, and mechanisms of action of that differ from antimuscarinic agents, appear interesting [13-15]. On the other hand, the optimization of OAB treatment regimens with currently used drugs and physical therapy may be a promising direction in this search, especially considering data on significantly high level of refusals from long-term therapy with antimuscarinics [16].

Previously, we studied the efficiency and safety of management of OAB in elderly men and women with combined high-dosed antimuscarinics. The results let us conclude that the proposed therapeutic regimen provided good therapeutic effects with an allowable level of increased side effects [17]. Previous research was followed by this study in which we set objectives to compare the maintenance effect of different therapeutic methods in elderly patients with a good initial result from the administration of antimuscarinics.

Detrusor overactivity in elderly women often correlates with the functional inconsistence of pelvic floor muscles and pelvic organs [18-20], which is why, in this study, we focused on researching the possibility of the long-term management of OAB symptoms in men over 65 years old without symptoms of prostatic hyperplasia and chronic urological inflammatory pathology.

METHODS AND MATERIALS

We selected at random 197 men (average age 68.7 years; from 65 to 77 years of age) with OAB. All patients received the most rational treatment according to the data of initial study: 60 mg of tropsium plus 40 mg of solifenacin daily, during 6 weeks. Satisfactory results were received in 181 patients (91.9%), after that they were distributed into 4 groups. Patients of Group A (49 persons) received trospium (60 mg daily) plus solifenacin (40 mg daily) during 1 month—the same as during basic therapy. Elderly men from Group B (41 person) received electrical stimulation of the detrusor according to the following procedure: active electrode (50 - 70 cm2) was applied above the pubis, an indifferent electrode (150 cm2) was applied in the lumbosacral area, Bernard's currents, frequency 20 Hz, depth of modulation 50 (75%), strength 20 to 40 mA, exposure time 15 minutes, with 15 procedures every other day [21-25]. Patients from Group C (43 persons) received laser punctures using helium-neon lasers (632.8 nm) applied to the projection of acupuncture points RP 6, RP 9, VC 2 during 1 to 1.5 minutes, to each point daily. The output power of light guide was 2 mW, with 30 procedures [26-29]. Group D (48 persons) was a control group. The cycle of maintenance therapy was conducted in 2.5 months after primary treatment.

The monitoring of patient conditions was performed clinically, through OAB-q questionnaires (during 1 year) [30,31] and using cystometry (before enrollment, in 6 and 12 months after primary treatment). The urodynamic state of the lower urinary tract was evaluated in accordance with the International Continence Society (ICS) guidelines [32-35]. Cystometry was performed using the urodynamic system "Relief-01" (DALPRIBOR, Vladivostok, Russia) with a double catheter microtip (UROBAR, Helmbrechts, Germany). The following data was recorded and analyzed: reflex volume (ml), bladder capacity (ml), and detrusor compliance (ml/cm H2O).

In accordance with research protocol, all patients who took part in the examination, less than 3 months prior to its beginning, underwent endoscopic examinations (cystoscopy) in order to exclude organic pathology. On the basis of cystoscopy, 7 patients were eliminated from the study.

Initial data were collected and processed with Microsoft Excel (Microsoft, Redmond, Washington, United States). Analysis was performed using JMP SAS Statistical Discovery 8.0.2 (SAS Institute, Cary, North Carolina, United States). Wilcoxon and Kruskal-Wallis tests were used to compare results in each treatment group during monitoring. One-way analysis of variance (ANOVAs) with the Tukey-Kramer method was used to compare effects in the groups. Standard deviation P values of < 0.05 were considered statistically significant.

The study was performed in accordance with good clinical practice and the Declaration of Helsinki. Prior written informed

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consent was obtained from each patient [32,33,35]. An examination and treatment diagram is shown in Figure 1.

RESULTS

Data on patient clinical and urodynamic indices in the course of basic and supportive treatment are shown in Figure 2 and Table 1 and Table 2. The best results among all groups were observed in Group A. The average number of daily incontinence events decreased after the initial cycle of antimuscarinics from 5.2 (1.3) to 1.3 (0.4) and remained consistently low at the sixth month, 1.5 (0.5), the ninth month, 1.5 (0.5), and the twelfth month, 1.9 (1.1), differing from the initial level with $P < 0.05$. Indices reflex volume, bladder capacity, and detrusor compliance showed improvements after the first cycle; after the second cycle of antimuscarinics these indices remained stable during all periods of monitoring. Also, a high correlation of main urodynamic and clinical indices (r - 0.6 ($P < 0.05$)) compared to IE with bladder capacity and detrusor compliance.

In Group B, satisfactory results were observed after 6 months of treatment; the clinical index of IE was at an allowably low level (2.0 (1.1)). The urodynamic indices also statistically differed from the initial. But by the ninth month almost all markers of the lower urinary tract showed reverse, negative development, and by the twelfth month they were close to initial indicators.

In Group C, the number of incontinence events by the sixth month was not statistically different from the initial level (3.4 (0.9)), and by the ninth month was almost identical to it. Urodynamic indicators of the lower urinary tract for patients of this group which, by the sixth month, differed from the initial level, though with minimal statistical significance they were somewhat unexpected.

In Group D, in which patients received a placebo, the number of incontinence events returned to the initial level by the sixth month of follow-up. Final urodynamic indicators were not different from the initial level as well.

As Table 1 shows, the tendency toward an increase of the indicator of post-void residual was observed in all monitored groups, but statistically significant differences were noted only between median values of the indicator in Group A compared before treatment and after the sixth month from its beginning.

In total, 31 patients reported side effects; among them 19 persons had poorly expressed side effects; therefore, the therapy was continued. The most common side effects included dry mouth (14), rash (2), flatulence (1), nausea (1), and dry and itchy skin (1).

Prior to examination all patients were informed orally and in writing about probable drug-related side effects (including

Figure 1. An algorithm of the examination and treatment of elderly men with OAB (before treatment: N = 197; after treatment: N =181).Note: The arrow shows the urodynamic tests (UDO); orange: the feature of reception solifenacin (40 mg) and trospium (60 mg); green: electrostimulation of the detrusor; pink: laser puncture; grey: receiving placebo.

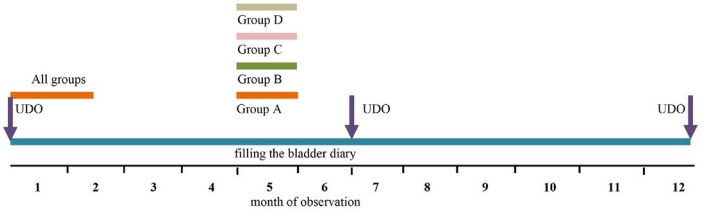
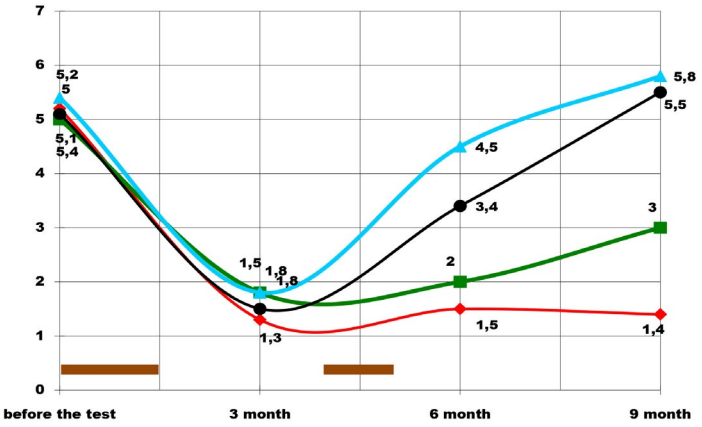


Figure 2. The frequency of episodes of incontinence in elderly men (before treatment: N = 197; after treatment: N = 181). Red: Group A (N = 49); Green: Group B (N = 41); Blue: Group C (N = 43); Black: Group D (N = 48). Horizontal lines indicate the time of the basic and supporting courses of treatment.



acute retention of urine), and the necessity to inform us immediately in case of the occurrence of side effects. During the follow-up period, acute urine retention events were observed in 3 cases (twice in the same patient). But at the time of consultation urine formation and urination function had restored spontaneously, and special drug therapy was not needed. After the examination of kidney functions and obtaining information about the absence of disorders, patients continued drug administration according to the schedule.

Table 1. Result of urodynamics (before treatment: N = 197; after treatment: N = 181).

Form of control	Indicators of urodynamics (± SD)											
Parameters of LUTS	Post-void residual (mL)			Reflex volume (mL)			Bladder capacity (mL)			Detrusor compliance (mL/cm H_2O)		
Time of study	Before	After[1]	After[2]	Before	After[1]	After[2]	Before	After[1]	After[2]	Before	After[1]	After[2]
Group A (N = 49)	17.5 (6)	29.5 (5.7)*	25.6 (7.9)	158.5 (37.6)	277.1 (44.2)**	266 (31.1)**	198 (25.6)	298.7 (45.6)**	293.4 (35.6)*	24.3 (3.4)	36.6 (5.4)*	33.9 (2.7)*
Group B (N = 41)	20.5 (7.9)	31.8 (11.8)	27.7 (5.3)	141.4 (30.5)	289.7 (34.5)**	196.4 (24.3)	185.6 (47.8)	301.5 (35.6)**	266,.7 (34.5)	19.8 (2.2)	33.6 (6.4)*	26.2 (2.6)*
Group C (N = 43)	2.,9 (4.9)	28.9 (9.1)	1.,8 (7.1)	148.2 (37.8)	267.6 (42.5)*	221.5 (76.5)	178.4 (47.4)	298.7 (34.3)*	187.6 (24.5)	20.5 (4.5)	34.4 (4.7)*	22.0 (7.3)
Group D (N = 48)	22.6 (6.6)	31.0 (6.3)	19.8 (8.5)	139.6 (35.6)	284.3* (34.4)	156.6 (32.3)	189.5 (34.6)	313.4 (47.3)*	199.8 (27.8)	25.2 (2.3)	35.6 (4.5)*	23.7 (4.8)

Remarks: SD, standard deviation; * < 0.05; ** < 0.001; Before, amounts taken at onset of study and considered baseline; After[1], 6 months from the start of the study; After[2], 12 months from the start of the study.

Table 2. Voiding diary data (before treatment: N = 197; after treatment: N = 181).

Form of control	Data diaries (± SD)					
Clinical parameters of LUTS	Incontinence events/day			Frequency of urination/ day		
Time of study	Before	After[1]	After[2]	Before	After[1]	After[2]
Group A (N = 49)	5.2 (1.3)	1.5 (0.5)**	1.9 (1.1)*	7.9 (1.3)	4.9 (1.1)*	5.3 (2.0)
Group B (N = 41)	5.0 (0.9)	2.0 (1.1)*	3.3 (1.0)	8.5 (0.7)	5.5 (1.3)*	7.5 (2.4)
Group C (N = 43)	5.1 (1.4)	3.4 (0.9)	4.7 (1.1)	8.1 (4.1)	6.4 (2.7)	7.9 (1.2)
Group D (N = 48)	5.4 (1.1)	4.5 (1.0)	5.5 (2.1)	6.9 (2.5)	6.0 (1.9)	6.8 (4.9)

Remarks: SD, standard deviation; * < 0.05; ** < 0.001; Before, amounts taken at onset of study and considered baseline; After1, 6 months from the start of the study; After2, 12 months from the start of the study.

During yearly follow-up study 12 patients (6.6%) stopped treatment and examinations: in 9 cases due to development of side-effects – intolerable dry mouth (7), flatulence (1), nausea, vomiting (1); in 3 cases treatment was discontinued due to circumstances not related to the treatment. In 4 cases treatment was discontinued in connection with lack of a positive effect.

DISCUSSION

We conducted a comparative analysis of the efficiency of several methods for maintenance therapy in elderly men having OAB who previously had demonstrated good therapeutic effects of treatment with combined antimuscarinics.

It was determined that the short cycle of treatment with 2 high-dosed antimuscarinics of different generations, conducted in 2.5 months after the main cycle, enables the maintenance of the initial clinical and urodynamic results for a long period of time (up to 1 year).

Positive results received in Group A, in our opinion, can be explained by the supposition that antimuscarinic agents synergistically activate suburothelial M2 and M3 receptors of the elderly male bladder with a "strengthening" effect and stabilization of their functional activity after repeated treatments after a small period of time [36-39].

Electrical stimulation of the urinary bladder and laser punctures as maintenance therapy, according to our data, proved to be less effective and cannot prevent the recurrence of the pathological symptoms of OAB. These methods, in particular, stimulate microcirculation and improve oxygenation of the detrusor, but it is insufficient for securing positive effects. Hypoxia of the urinary bladder wall tissue is not a leading mechanism in the development of OAB, and the absence of specific influences on receptors results in weak and short-term effects.

CONCLUSION

A short cycle of treatment with 2 high-dosed antimuscarinics (trospium and solifenacin), conducted in 2.5 months after

the main cycle, significantly decrease the probability of OAB recurrence during 1 year with a low level of side effects. An application of electrical stimulation of the detrusor and laser puncture does not ensure the maintenance of positive effects of pharmaceutical therapy. Further studies are required to determine necessary terms for repeated cycles of maintenance and pharmaceutical treatment of OAB in elderly men in the period exceeding 1 year.

MAIN CONCLUSION

Repeated treatment of OAB with a combination of high-dosed antimuscarinics is an effective method for reducing the risk of recurrence of the disease in elderly men.

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