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Research Article



Effectiveness of treatment of detrusor overactivity after transurethral resection of benign prostate hyperplasia

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BACKGROUND: In a significant number of patients with benign prostatic hyperplasia who underwent transurethral resection (TURP), micturition disorders are detected in the late postoperative period. The issues of drug treatment of overactive bladder are widely covered in the literature and clinical guidelines. However, the number of studies on the treatment of patients with detrusor overactivity after TURP is relatively small.

AIM: The aim of the study is to increase the effectiveness of treatment of patients with detrusor overactivity after TURP in the late postoperative period.

MATERIALS AND METHODS: We treated 51 patients with urodynamically confirmed detrusor overactivity after TURP aged 56 to 87 years (mean 71.5 ± 8.4 years). Taking into account the comorbid background, concomitant therapy, age characteristics and the presence of contraindications, 8 patients were prescribed solifenacin, 9 — trospium chloride, 34 — mirabegron. Appointment of anticholinergic therapy for 1 month in 7 patients was ineffective, they were prescribed mirabegron. Drug treatment lasted 3 months. With insufficient effectiveness of drug therapy, combined treatment with mirabegron was performed in combination with extracorporeal magnetic stimulation (ECMS) for 1 month (12 sessions of ECMS in total). When the combination of ECMS and mirabegron was ineffective, intravesical botulinum therapy was performed. The effectiveness of treatment was assessed by subjective assessment by patients, the results of patients filling out IPSS questionnaires, urination diaries, ultrasound results and uroflowmetry.

RESULTS: After the end of drug therapy 17 (33.3%) patients subjectively rated the result of treatment as “excellent”, 15 (29.4%) patients as “good”. In 19 (37.3%) patients the effectiveness of drug therapy was regarded as insufficient and they underwent combined therapy with mirabegron and ECMS. As a successful combination therapy was recognized in 10 (52.6%) patients. Botulinum therapy was performed in 6 patients with ineffectiveness of the previous stages of treatment with a positive effect in 5 (83.3%) of them. Tolerability of treatment was satisfactory. Based on the results of the study, an algorithm for the treatment of detrusor overactivity in patients with urination disorders in the late postoperative period after TURP was proposed.

CONCLUSIONS: The applied treatment regimen for patients with detrusor overactivity after TURP is effective and can be recommended for use in clinical practice.

Keywords: benign prostatic hyperplasia; bladder outlet obstruction; lower urinary tract symptoms; transurethral resection of the prostate; extracorporeal magnetic stimulation; detrusor overactivity; overactive bladder.

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Научная статья

Эффективность лечения гиперактивности детрузора после трансуретральной резекции доброкачественной гиперплазии предстательной железы

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Актуальность. У значительного числа больных доброкачественной гиперплазией предстательной железы, перенесших трансуретральную резекцию, в отдаленном послеоперационном периоде выявляют расстройства мочеиспускания. Вопросы медикаментозного лечения гиперактивности мочевого пузыря широко освещены в литературе и клинических рекомендациях. При этом количество исследований, посвященных лечению пациентов с гиперактивностью детрузора после трансуретральной резекции предстательной железы, относительно невелико.

Цель — повышение эффективности лечения пациентов с гиперактивностью детрузора после трансуретральной резекции в отдаленном послеоперационном периоде.

Материалы и методы. Пролечен 51 пациент с уродинамически подтвержденной гиперактивностью детрузора после трансуретральной резекции предстательной железы в возрасте от 56 до 87 лет (в среднем $71,5 \pm 8,4$ года). Учитывая коморбидный фон, сопутствующую терапию, возрастные особенности и наличие противопоказаний 8 пациентам назначали солифенацин, 9 — троспия хлорид, 34 — мирабегрон. Терапия М-холиноблокаторами в течение 1 мес. у 7 больных оказалась неэффективной, им был назначен мирабегрон. Медикаментозное лечение длилось 3 мес. При недостаточной эффективности медикаментозной терапии проводили комбинированное лечение мирабегроном в сочетании с экстракорпоральной магнитной стимуляцией в течение 1 мес. (всего 12 сеансов). При неэффективности данной комбинации проводили внутривезикулярную ботулинотерапию. Эффективность лечения оценивали посредством субъективной оценки пациентами, результатов заполнения больными опросников IPSS, дневников мочеиспускания, результатов ультразвукового исследования и урофлоуметрии.

Результаты. После окончания медикаментозной терапии 17 (33,3 %) пациентов субъективно оценили результат лечения как «отличный», 15 (29,4 %) — как «хороший». У 19 (37,3 %) пациентов эффективность медикаментозной терапии была расценена как «недостаточная» и им была проведена комбинированная терапия мирабегроном и экстракорпоральной магнитной стимуляцией. Как «успешная» комбинированная терапия была признана у 10 (52,6 %) пациентов. Ботулинотерапию проводили 6 пациентам с неэффективностью предыдущих этапов лечения с положительным эффектом у 5 (83,3 %) из них. Переносимость лечения была удовлетворительная. На основе результатов проведенного исследования предложен алгоритм лечения гиперактивности детрузора у пациентов с расстройствами мочеиспускания в отдаленном послеоперационном периоде после трансуретральной резекции предстательной железы.

Выводы. Примененную схему лечения пациентов с гиперактивностью детрузора после трансуретральной резекции предстательной железы можно считать эффективной и рекомендовать для использования в клинической практике.

Ключевые слова: доброкачественная гиперплазия предстательной железы; инфравезикальная обструкция; симптомы нижних мочевыводящих путей; трансуретральная резекция предстательной железы; экстракорпоральная магнитная стимуляция; гиперактивность детрузора; гиперактивный мочевой пузырь.

Как цитировать:

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BACKGROUND

Despite advances in conservative therapy, surgical methods for the treatment of patients with benign prostatic hyperplasia (BPH) continue to be widely used and actively developed [1]. Transurethral resection of the prostate (TURP) is a time-proven gold-standard surgical intervention to eliminate infravesical obstruction in BPH, and the analysis of long-term TURP results in patients with BPH proves its high efficiency [2, 3]. Moreover, lower urinary tract symptoms persist in 5%–49% of patients who underwent TURP [4–7]. According to researchers, detrusor overactivity (DO) is detected in 9.6%–40% of patients with urination disorders following prostate surgery [8–10].

The issues of the efficacy and safety of drug therapy for overactive bladder are widely covered in the literature and clinical guidelines [1, 11, 12]. However, the number of studies on the efficiency of DO therapy following prostate surgery is relatively small [4, 5, 13]. This is largely because in most of the studies on the treatment of overactive bladder, a history of surgery on the lower urinary tract and prostate is an exclusion criterion [11, 14, 15]. The vast majority of patients with urinary disorders following TURP are older ones and patients with senility who require a special approach when prescribing the therapy [16, 17]. Thus, the determination of an approach for the treatment of urinary disorders following TURP is a very urgent problem in modern urology.

This study aimed to increase the efficiency of the treatment of patients with DO following TURP in the late postoperative period.

MATERIALS AND METHODS

The study included 51 patients with BPH who had a history of TURP and aged 56–87 (mean age 71.5 ± 8.4) years. According to cystometry data, DO was detected in all patients. The study included 7 (13.7%) patients aged <60 years, 15 (29.4%) aged 60–70 years, 21 (41.2%) aged 71–80 years, and 8 (15.7%) aged >80 years.

The inclusion criteria were a history of TURP for BPH, lack of data on intraoperative and early postoperative complications of TURP, presence of DO according to urodynamic studies, and signed informed consent to participate in the study.

The exclusion criteria were a history of prostate or bladder cancer, radiation therapy of the pelvic region, urinary incontinence before TURP, surgical interventions on the pelvic organs other than TURP, acute or exacerbated chronic urinary tract infections, and inability to follow the doctor's instructions due to impaired physical, cognitive, or psychoemotional status.

After signing an informed consent to participate in the study, severity of symptoms, quality of life (QoL), and

long-term results of TURP were assessed, and patients answered the International Prostate Symptom Score (IPSS) questionnaire and the QoL questionnaire, filled out a urination diary for 3 days, underwent ultrasound examination of the kidneys, prostate gland, and bladder with the determination of residual urine, uroflowmetry, and voiding cystometry.

For a subjective assessment of the treatment efficiency, patients chose the response options “excellent treatment outcome” (disappearance or obvious improvement in urination disorders), “good treatment outcome” (significant reduction in urination disorders), “satisfactory treatment outcome” (moderate decrease in urination disorders), and “ineffective treatment.” The criterion for treatment efficiency, in addition to subjective assessment by patients, was a decrease in the total IPSS and QoL scale scores by >30% and a decrease in the frequency of urination and/or urgency/urge urinary incontinence according to the urination diary by >30%.

The terminology, equipment, and methods for conducting urodynamic studies corresponded to the recommendations of the Standardization Committee of the International Continence Society (ICS, 2019) [18].

The selection of drug therapy for DO must consider the patient's age, comorbidities and therapy, anticholinergic burden, and presence of cognitive disorders [16, 17, 19]. M-cholinoblockers were prescribed to patients aged ≤ 65 years with an anticholinergic burden of 0–1 point on the anticholinergic cognitive burden scale, absence of cognitive impairment, and contraindications to anticholinergic therapy; eight patients received solifenacin at a dose of 10 mg once daily, and nine patients received trospium chloride at a dose of 15 mg three times daily. The remaining 34 patients received mirabegron at a dose of 50 mg once daily. After 1 month of treatment, M-cholinoblockers were ineffective in seven patients; in these patients, anticholinergic therapy was canceled, and mirabegron was prescribed at a dose of 50 mg once daily. The total duration of drug therapy was 3 months. After this therapy, improvement was recorded in 32 (62.7%) patients. No significant effect was noted in 19 (37.3%) patients who continued the combined treatment with mirabegron and extracorporeal magnetic stimulation (ECMS). The latter was performed on the Avantron device (Rehabilitation Technologies, Russia) for three sessions per week with a course of 12 procedures. The magnetic stimulation frequency was 10 Hz with a magnetic field strength of 0.5 Tesla and a stimulation time of 20 min. If conservative therapy was ineffective, the patients received intradetrusor injections of onabotulinum toxin type A at a dose of 100 IU (5 IU at 20 points). Botulinum therapy was performed in six patients with DO who participated in this study.

Statistical processing of the study results was performed using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA). The minimum, maximum, and average values of the indicators, their root-mean-square deviation, and mean square error were determined. Differences were considered significant at $p < 0.05$.

RESULTS

Following the drug therapy, 17 (33.3%) patients subjectively assessed the treatment outcome as “excellent,” 15 (29.4%) rated it as “good,” 8 (15.7%) considered it “satisfactory,” and 11 (21.6%) indicated its ineffectiveness (Fig. 1). Thus, 32 (62.7%) patients rated the result of drug therapy as “excellent” or “good.”

Following the drug therapy, the severity of urination disorders decreased (Table 1). The total score on the IPSS scale decreased from 24.2 ± 1.1 to 14.7 ± 0.7 ($p < 0.05$), which was accompanied by an improvement in the QoL; thus, the average score on the QoL scale decreased from 4.6 ± 0.2 to 3.9 ± 0.1 ($p < 0.05$). According to urination diaries, the frequency of daytime and nocturnal urination also decreased significantly. During treatment, no

significant change was observed in the urine flow rate, residual urine volume, and prostate gland volume.

Combined treatment with ECMS and mirabegron was initiated in patients in whom the efficiency of drug therapy was insufficient. Moreover, 10 of the 19 (52.6%) patients who received this treatment subjectively assessed the treatment results as “excellent,” “good,” or “satisfactory,” whereas 9 (47.4%) patients indicated the absence of significant improvement (Fig. 2).

Table 2 presents the dynamics of clinical parameters in patients with DO before and after the combined treatment with ECMS and mirabegron.

Following the combined treatment, the mean IPSS score decreased from 19.9 ± 0.6 to 15.3 ± 0.9 ($p < 0.05$), and the QoL due to urinary disorders improved, that is, the QoL scale score decreased from 4.1 ± 0.2 to 2.7 ± 0.1 points ($p < 0.05$). According to the urination diary, the frequency of daytime urination and the frequency of urgency decreased significantly (Table 2). No changes were observed in the maximum urination rate and residual urine volume following the combined treatment with ECMS and mirabegron, that is, bladder emptying did not worsen during the treatment.

Table 1. Dynamics of clinical parameters in patients with detrusor overactivity before and after drug therapy ($n = 51$)

Таблица 1. Динамика клинических показателей у больных с гиперактивностью детрузора до и после медикаментозной терапии ($n = 51$)

Clinical indicator	Before treatment	After treatment
IPSS, score	24.2 ± 1.1	$14.7 \pm 0.7^*$
QoL, score	4.6 ± 0.2	$3.9 \pm 0.1^*$
Number of daytime urinations per day	11.3 ± 0.3	$8.3 \pm 0.3^*$
Number of nocturnal urinations per day	2.8 ± 0.2	$1.1 \pm 0.1^*$
Number of imperative urges, per day	4.7 ± 0.3	$2.4 \pm 0.1^*$
Number of episodes of urge urinary incontinence, per day	2.3 ± 0.2	$0.8 \pm 0.1^*$
Maximum urine flow rate (Q_{max}), mL/s	17.8 ± 0.6	16.2 ± 0.5
Prostate volume, cm^3	37.1 ± 1.7	36.4 ± 1.8
Residual urine volume, mL	23.2 ± 2.1	36.7 ± 1.9

*Significant differences compared with the pretreatment score ($p < 0.05$).



Fig. 1. Subjective assessment by patients with detrusor overactivity of the results of drug therapy ($n = 51$)

Рис. 1. Субъективная оценка результатов медикаментозной терапии пациентами с гиперактивностью детрузора ($n = 51$)



Fig. 2. Subjective assessment by patients with detrusor overactivity of the results of combined treatment ($n = 19$)

Рис. 2. Субъективная оценка пациентами с гиперактивностью детрузора результатов комбинированного лечения ($n = 19$)

Table 2. Dynamics of clinical parameters in patients with detrusor overactivity before and after combined treatment ($n = 19$)**Таблица 2.** Динамика клинических показателей у больных с гиперактивностью детрузора до и после комбинированного лечения ($n = 19$)

Clinical indicator	Before treatment	After treatment
IPSS, score	19.9 ± 0.6	15.3 ± 0.9*
QoL, score	4.1 ± 0.2	2.7 ± 0.1*
Number of daytime urinations per day	9.4 ± 0.3	8.5 ± 0.3*
Number of nocturnal urinations per day	1.1 ± 0.2	0.8 ± 0.1
Number of imperative urges per day	2.3 ± 0.1	1.6 ± 0.1*
Number of episodes of urge urinary incontinence per day	0.7 ± 0.2	0.4 ± 0.1
Maximum urine flow rate (Q_{max}), mL/s	15.5 ± 0.6	15.9 ± 0.5
Prostate volume, cm ³	37.1 ± 1.5	36.8 ± 1.5
Residual urine volume, mL	35.2 ± 2.2	33.6 ± 2.5

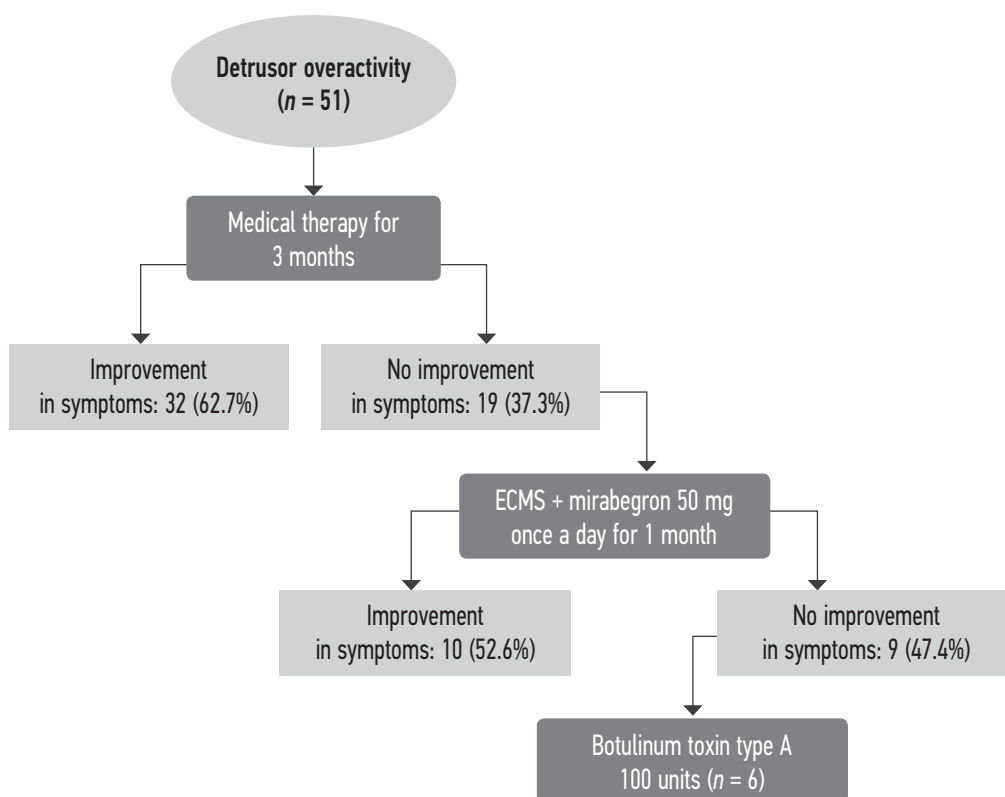
*Significant differences compared with the pretreatment score ($p < 0.05$).

In six patients in whom the efficiency of the combined treatment was insufficient, intravesical botulinum therapy was performed, which turned out to be effective in 5 (83.3%) of the treated patients.

Based on the study results, we proposed an algorithm for the treatment of DO in patients with urination disorders in the late postoperative period following TURP (Fig. 3). This implies that before treatment initiation, all patients should undergo a comprehensive urodynamic

examination to assess the nature of the lower urinary tract dysfunction.

When prescribing drug therapy to patients with DO, patient age, presence of concomitant diseases, cognitive status, degree of anticholinergic burden, and presence of contraindications for prescribing M-cholinoblockers must be taken into account. We consider drug therapy as initial in patients with DO following TURP in the late postoperative period. Owing to its ineffectiveness, combined

**Fig. 3.** Algorithm and results of detrusor overactivity treatment in patients after TURP**Рис. 3.** Алгоритм и результаты лечения пациентов с гиперактивностью детрузора после трансуретральной резекции предстательной железы

treatment with ECMS and mirabegron at standard dosage is reasonable. If urination disorders persist following conservative treatment, the intradetrusor administration of botulinum toxin type A is indicated. In this study, patients tolerated the treatment satisfactorily, and no adverse events were registered.

DISCUSSION

The efficiency of treatment of patients with DO following surgery on the lower urinary tract remains a largely unexplored issue [9, 14, 15]. In most studies evaluating the efficiency of DO therapy, surgeries on the lower urinary tract are considered an exclusion criterion [11]. Few studies have investigated the efficacy and safety of DO therapy in patients in the late postoperative period following TURP. In this study, the mean age of the patients was 71.5 years, and most patients ($n = 29$ [56.9%]) were over 70 years old. M-cholinoblockers or β 3-adrenergic agonists are recommended as the first-line treatment for an overactive bladder [1]. When prescribing drug therapy, patient age, probability of cognitive impairment, concomitant therapy, and comorbid background should be considered [16, 17, 19]. In this study, eight patients received solifenacin, and nine received tiroprium chloride. M-cholinoblockers were prescribed in patients aged <65 years, the anticholinergic burden index did not exceed 1 point, and the patient had no cognitive impairments and concomitant diseases in which drug prescription is contraindicated (angle-closure glaucoma, etc.). The remaining 34 patients started treatment with mirabegron, which does not have the above contraindications. This approach enabled us to effectively perform DO therapy with a minimum number of side effects. With the ineffectiveness of the above drug therapy, an option for further treatment is the prescription of combined treatment with M-anticholinergics and mirabegron. However, the characteristics of the patient population (older and senile age, cognitive impairment, concomitant therapy, and risk of polypharmacy) did not allow for the prescription of the combined treatment with M-cholinoblockers and mirabegron with the proper level of safety and patient compliance. Therefore, in such patients, a combination of mirabegron and ECMS was used as second-line therapy.

When using ECMS, compared with drug therapy, pathogenetic mechanisms of therapeutic action in DO are involved. The effect of the low frequencies of an alternating magnetic field (5–10 Hz) on the pudendal nerve causes excitation of its afferent fibers, decreased tone of urination centers, and inhibited activity of the efferent parasympathetic pathways, but increased sympathetic activity in the efferent pathway of the hypogastric nerve. The above processes inhibited the involuntary contractions of the detrusor [20]. Another mechanism of ECMS action is the stimulation of the sacral nerves and

activation of the inhibitory interneuronal reflex. Moreover, the activity of type C nerve fibers, which affect the increase in bladder tone, is inhibited [20].

With the combined treatment, a positive effect from the use of ECMS and mirabegron was recorded in 10 of 19 patients who had not previously responded to the above drug therapy. Considering that these patients did not respond to drug therapy earlier, we regard the result as quite successful.

The results of this study indicate the high efficiency of conservative DO therapy in patients who underwent TURP; therefore, we can propose an algorithm for the treatment of such patients.

The prescription of mirabegron and solifenacin (in the absence of contraindications) led to a significant decrease in the severity of urinary disorders in patients who underwent TURP. In this regard, we recommend the use of mirabegron or M-cholinoblockers as first-line therapy in DO, and if drug therapy was ineffective, combined treatment with ECMS and mirabegron should be used. If urinary disorders persist following conservative treatment, in our opinion, the intradetrusor administration of botulinum toxin type A is indicated.

Older people with senility and DO are at an increased risk of falls owing to frequent toileting, especially at night. Falls cause 90% of hip fractures and are the fifth leading cause of death among older individuals. The successful and effective treatment of DO can reduce this risk and improve life expectancy and QoL in these patients [21, 22].

At the end of treatment, the severity of symptoms of urination disorders decreased. Accurate determination of the cause of urinary disorders following TURP, in this case DO, became the basis for the correct drug prescription, and the treatment was highly effective and safe.

CONCLUSIONS

DO is a common cause of micturition problems in patients with a history of TURP. Clarifying the causes of dysuria according to the comprehensive urodynamic study enabled us to prescribe a pathogenetically substantiated therapy for patients with urinary disorders following TURP. We developed an algorithm for treating urination disorders following TURP due to DO, which complies with clinical guidelines and global literature data. The high clinical efficacy and good tolerability of the treatment enable us to recommend the proposed therapeutic algorithm for use in wide clinical practice for treating DO in patients with a history of TURP.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article,

final approval of the version to be published and agree to be accountable for all aspects of the study. Contribution of each author: R.N. Simanov — the idea of writing an article, the concept and design of the study, literature review, data collection and clinical materials, information processing, text writing and preparation of illustrative material; R.E. Amdiy — assistance in drafting the design and concept of the study, scientific support, collection and processing of information, assistance in writing text, correction of the final version of the manuscript; S.Kh. Al-Shukri — scientific support, collection and processing of information, correction of the final version of the manuscript; I.V. Kuzmin — assistance in

drawing up the design, the concept of research and in writing the text of the manuscript; O.Yu. Barysheva — assistance in writing and correcting the text of the manuscript, preparation of documentation for the publication of the manuscript.

Competing interests. The authors declare that they have no competing interests.

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Ethics approval. The study participants were informed about the objectives and methodology of the study and voluntarily provided written consent for their participation.

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