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Combination therapy in the integrated treatment of recurrent chronic cystitis

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Abstract

Aim. To assess the results of the integrated treatment of women with recurrent chronic cystitis using the selective β_3-adrenoreceptor (AR) agonist, mirabegron.

Methods. The results of the treatment of women diagnosed with recurrent chronic cystitis in the urological clinic of KSMU were analyzed. The average age of patients was 31.5±3.4 years. To assess the effectiveness of integrated treatment, women with recurrent chronic cystitis were randomly divided into two groups: the first group (30 patients) who received antibiotic therapy in combination with the drug mirabegron at a dose of 50 mg once a day and the second (control) group (30 patients), who received antibiotic therapy taking into account their susceptibility. All patients underwent ultrasonography of the genitourinary system, urodynamic studies with assessment of the maximum urinary flow, average urinary flow, bacterial urine cultures.

Results. Analysis of the research results showed a greater reduction in the number of urinations per day (up to 7 times) in the first group. The frequency of urinary urgency decreased in 82.6% of the first group patients compared to 64% of the second group ($p < 0.05$). In the combination therapy versus control groups, there was reduced hospital stay by an average of 4 days (11.2 vs 15 days; $p < 0.05$). On the 15th day of treatment, control cystoscopy revealed no changes in the bladder mucosa in all patients of the first group. Also, in the first group of patients, there was a greater improvement in urodynamic parameters compared to the control group ($p < 0.05$).

Conclusion. The selective β_3-AR agonist mirabegron used in the integrated treatment of recurrent chronic cystitis increases the effectiveness of the therapy.

Keywords: recurrent chronic cystitis, mirabegron, urodynamics.

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Background

Recurrent chronic cystitis is a serious condition that is more common in women, requiring long-term treatment and subsequent dynamic monitoring in order to prevent its recurrence. Urinary tract infections remain an urgent problem not only because of their prevalence and frequent relapses, but also due to their impact on physical health and the emotional sphere of life. A standard treatment of recurrent chronic cystitis should be comprehensive, taking into account the etiology and pathogenesis of the disease.

Approximately 50% of adult women have had at least one clinical appearance of urinary tract infection during their lifetime [1]. In addition, half of them developed recurrent uncomplicated urinary tract infection in the next 6–12 months. Furthermore, 50% of women experience relapses more than 3 times a year [2].

According to the National Hospital Ambulatory Medical Care Survey, 7 million cases of urinary tract infections are registered in the US medical practice yearly, and more than 2 million patients with cystitis are hospitalized [3]. In the UK, 2.5 million women report signs of urinary disorders, and more than 100 thousand of them are diagnosed with recurrent urinary tract infections. In Russia, one third of young women develop a clinical picture of relapse within 6 months, and 50% of patients have relapses more than 3 times a year [3].

An important aspect regarding chronic recurrent cystitis is that it occurs in most cases (up to 40%) among women of a working age (20–40 years) [4, 5], and in 50% of cases, it leads to a disbalance and loss of efficiency [6, 7] and the development of a neurosis-like state, depriving them of a full night's sleep and habitual lifestyle [8]. In this regard, the problem has a great social significance,

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which requires the search for new effective methods of treatment.

The age and sex of the patient are important factors for the development of the disease [2]. The disease occurs in 5% of patients of a childbearing age, 10%–15% of patients in the menopausal period, and 15%–20% of patients in the elderly age [2]. Risk factors for the development of the symptoms of lower urinary tract diseases are functional and anatomical disorders, childhood infections, frequent changes of sexual partners, violation of the urodynamics of the lower urinary tract, low level of hygiene, use of contraceptives containing spermicides, and concomitant gynecological diseases [2].

It is assumed that the loss of glycosaminoglycans of the bladder mucosa plays a major role in the development of symptoms that in turn leads to increased contractile detrusor function [9, 10].

Currently, there is no single treatment strategy for the urinary disorders of patients with chronic cystitis [2]. According to the literature, the clinical features of women with chronic cystitis are associated with microcirculatory, morphological, and urodynamic disorders and an increase in the level of biologically active substances in urine that affect the bladder receptors. As a result, persistent dysuria occurs, and the inflammatory process in the bladder wall and its hyperactivity are maintained [11]. For these reasons, the treatment of chronic cystitis should be complex, involving the use of various groups of drugs. The selective agonist of β3-adrenoreceptors mirabegron serves as a means that improves the reservoir function of the bladder by stimulating the β3-adrenoreceptors located in its wall.

This study aimed to study the effectiveness of mirabegron in the complex treatment of patients with recurrent chronic cystitis.

Materials and methods

From 2018–2019, the urological clinic of Kazan State Medical University treated 60 patients with a diagnosis of recurrent chronic cystitis whose average age was 31.5 ± 3.4 years. The patients presented complaints of frequent painful urination in small volumes, supra-pubic pain, lower abdominal discomfort, and imperative urges to urinate. All the women had been having this condition for 3–7 years.

The patients underwent a standard examination algorithm including:

– general blood tests;

– general urine analysis;

– urinary microbiological examination with determination of the sensitivity to antibacterial drugs;

– biochemical analysis of blood;

– ultrasound examination of the genitourinary system;

– uroflowmetry with determination of the residual urine volume;

– urodynamic studies with an assessment of the maximum urinary flow rate and average speed of urination;

– filling urine registration diaries for 3 days;

– x-ray examinations according to indications.

The inclusion criteria to participate in this study include frequent urination >10–15 times a day, residual urine volume ≤100 ml, painful urination, imperative urge to urinate, confirmed diagnosis of "chronic recurrent cystitis" (more than a year), leukocyturia, and the presence of 10^3 colony-forming units of microbial pathogens in 1 ml.

The exclusion criteria include neurogenic bladder, bladder tumors and stones, radiation cystitis, pregnancy, the use of drugs that affect the symptoms of chronic cystitis, urinary incontinence, decompensated diabetes, and gynecological diseases during the last 3 months.

The patients who met the inclusion criteria were randomly divided into two groups of 30 patients. The study groups were comparable in age, clinical and laboratory data, anamnesis data, and clinical features; these indicators were quite identical in both groups. Patients in the first group were prescribed mirabegron at a standard dose of 50 mg in combination with antibacterial therapy, taking into account the sensitivity to the antibacterial drug. The second group was the control group, which included 30 patients who received antibacterial therapy, taking into account the sensitivity of isolated microorganisms according to the bacterial urine culture. The observation period of the study participants was 30 days.

The comparability of the groups according to the initial indicators is shown in tables 1 and 2.

Antibacterial therapy was administered for 10 days. Mirabegron 50 mg was taken once a day for 1 month as a symptomatic therapy to reduce the symptoms of the lower urinary tract damage.

The effectiveness of the mirabegron treatment in the first group in comparison with the second group was evaluated on day 15 and 1 month after the start of the treatment.

Quantitative indicators were compared using the Welch t-test, and the Fischer's exact test was used to compare the qualitative indicators. To assess the statistical significance of the differences in the dependent indicators, we used a variance analysis with repeated measurements. The differences were considered statistically significant at $p < 0.05$. The study materials included data obtained in the course of the patients' laboratory studies.

Table 1. Characteristics of the initial indicators of the patients

Indicators	First group, n = 30	Second group, n = 30	p
Age of patients, years	32.3±3.9	30.9±2.8	0.1476
Duration of chronic cystitis, years	5 (4; 5.75)	5 (4; 6)	0.5903
Bacteriuria ≤10^3 CFU/ml	16	15	≈1
Bacteriuria >10^3 CFU/ml	14	15	≈1
Frequent urination ≤18 times/day	9	10	≈1
Frequent urination ≤6 times/day	21	20	≈1
Urgent tenesmus ≤30 times/day	16	14	0.7963
Urgent tenesmus ≤26 times/day	14	16	0.7963

Note: CFU are colony-forming units.

Table 2. Characteristics of the initial data from the cystoscopy results

Cystoscopy data	First group, n = 30	Second group, n = 30	p
Diffuse hyperemia	8	9	≈1
Puffiness of the mucous membrane	13	11	0.7921
Changes in the Lieto triangle	18	16	0.7945
Trabekuliarnae mucosa	26	27	≈1

Table 3. The main bacterial pathogens of recurrent chronic cystitis according to the bacterial culture results before treatment (%)

Pathogen	First group, n = 30	Second group, n = 30	p
Escherichia coli	75.1	74.2	0.91
Proteus mirabilis	5.8	4.7	0.91
Klebsiella pneuoniae	7.1	7.8	0.91
Staphilococcus epidermidis	5.9	5.8	0.91
Enterococcus spp.	5.3	6.6	0.91
Others	0.8	0.9	0.91

Results and discussion. Upon admission to the hospital, a pathogenic microflora was detected for all the patients (table 3).

Analysis of the data presented in table 3 did not reveal any statistically significant differences in the structure of the bacterial pathogens of chronic recurrent cystitis among the patients of the study groups ($p = 0.91$).

In the course of treatment, patients of the main and control groups registered a positive dynamic expression of symptoms. However, for the patients of the main group on the background of the combined mirabegron treatment, these changes had an increased expression ($p < 0.05$).

In the combination therapy group, on the 15th day of treatment, there was a significant decrease in the frequency of urination to ≤7 times/day for 27 (90%) patients of the main group and ≤10 times/day for 23 (76.6%) patients of the second group ($p<0.05$). There was also a decrease in the number of urgent tenesmus to ≤5 times/day for 25 (83.3%) patients of the first group and ≤11 times/day for 19 (63.3%) patients of the second group ($p < 0.05$) according to the urination diaries.

After 30 days of treatment, there was a decrease in the frequency of urination to ≤5 times/day for 29 (96.6%) patients of the first group and ≤7 times/day for 28 (93.3%) patients of the second group. There was also a decrease in the number of urgent tenesmus to ≤3 times/day for 27 (90%) patients of the first group and ≤8 times/day for 24 (80%) patients of the second group according to the urination diaries. The data is shown in figures 1 and 2.

The cystoscopy picture in the first and second groups before the treatment was typical for recurrent chronic cystitis. In both groups, diffuse hyperemia was present throughout the bladder mucosa, as well as the presence of edema with the deposition of fibrin films and hemorrhagic zones in the Lieto triangle area and trabecularity of the bladder mucosa.

Control cystoscopy on the 15th day of treatment revealed no changes in the first group for all the patients. In the second group, 6 (20%) patients had persistent trabecularity of the bladder mucosa, which indicated that the detrusor tone remained elevated.

Before treatment, according to the ultrasound data, 16 (53.3%) patients of the first group had a residual urine volume of 65.7 ± 0.2 ml after urination, and 18 (60%) patients of the second group had the same residual urine volume.

After 30 days of treatment, only 1 (3.3%) woman in the mirabegron treatment group was found to

Table 4. Dynamics of the uroflowmetry indicators in the treatment process

Indicator	Before treatment		Day 15		Day 20		p
	Main group	Control group	Main group	Control group	Main group	Control group	
TQ, s	6.9±0.5	6.7±0.4	7.7±0.4	7.4±0.4	8.7±0.2	8.0±0.3	0.041
Q_{Max}, ml/s	37.3±0.5	37.5±0.6	35.2±0.4	35.9±0.5	30.1±0.1	33.2±0.3	0.038
V_{Comp}, ml	102.3±3.1	104.1±2.5	122.1±2.3	125.2±2.1	138.1±1.8	132.0±1.8	0.016

Note: TQ, time to reach the maximum rate of urination; QMax, the maximum rate of urination; V_{Comp}, the volume of urine released.

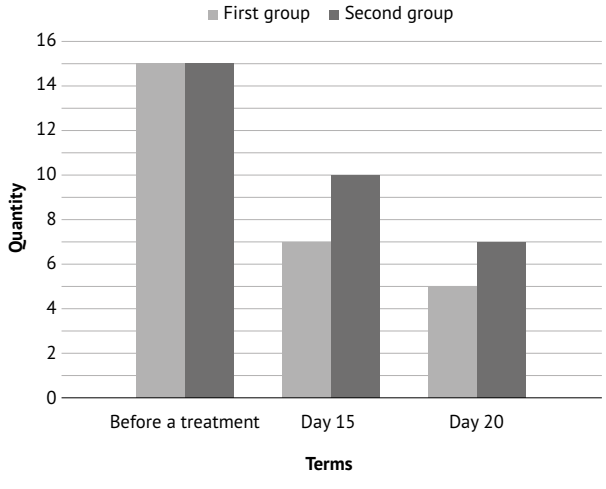

Fig. 1. Frequency of urination according to the urination diaries

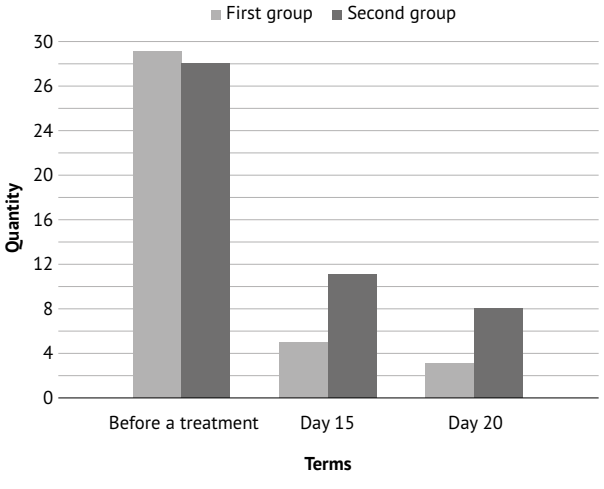

Fig. 2. The number of urgent tenesmus according to the voiding diaries

have a residual urine volume of 58 ml. In the second group, 6 (19.3%) patients retained a residual urine volume of 67.5 ± 0.3 ml, which confirmed the presence of a symptom of urinary disorders (p =0.0443).

Urodynamic studies were conducted to determine the maximum and average speed of urination. Dynamic monitoring of the patients for 15 and 30 days of treatment showed an improvement in the urodynamics of the lower urinary tract. Prior to treatment, all the patients had an increased maximum urine flow rate, a decreased urination volume, and a shortened urination time. During treatment, an increase in the duration and volume of urination and a decrease in the maximum volume rate of urine flow was significantly expressed in the group of patients who took mirabegron. Indicators of the urination rate of the first and second groups before and after treatment are presented in table 4.

As shown by the results of our study, the complex therapy administered to the patients of the first group was more effective compared to that of the second group. The length of hospital stay in the first group was reduced by 4 days compared to the second group (11.2 and 15 days, respectively; p = 0.005).

The results obtained confirm the feasibility of including mirabegron in the complex therapy for recurrent chronic cystitis.

Conclusion

Mirabegron, a drug used in the complex therapy, according to our observation, increases the effectiveness of the treatment of recurrent chronic cystitis, improves urodynamic parameters, contributes to the normalization of the frequency of urination and the disappearance of imperative urges, and reduces the length of hospitalization.

Authors' contributions. D.R.S., coordinated the study and conducted the research; A.U.Z. responsible for collecting and analyzing the data.

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Conflict of interest. The authors declare no conflict of interest.

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