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New approaches to the treatment of patients with an overactive bladder and non-obstructive urge urinary incontinence

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Abstract: Overactive bladder (OAB) occurs in 20% of patients with various urinary disorders, while urge urinary incontinence is detected among a third of these patients. The goal of the work was to improve the results of treatment of women suffering from OAB with urge urinary incontinence and non-obstructive urination, by using a combination of drugs - an α1-adrenergic blocker and an M-anticholinergic blocker; study of the relationship between clinical and urodynamic manifestations of the disease. The state of microcirculation of the bladder mucosa was also studied before and after treatment. We examined and treated 40 women from 17 to 69 years old with a disease duration of one to 20 years. The patients were prescribed a combination of the α1-adrenergic blocker tamsulosin 0.4 mg at night and the M-anticholinergic blocker oxybutynin 5 mg in the morning daily for a month. After treatment, according to uroflowmetry and cystometry, the time of urination was shortened, the volume of urination increased and the maximum volumetric flow rate of urine increased; in addition, the cystometric capacity increased; involuntary detrusor contractions during the bladder filling phase (spontaneous or provoked) became fewer or were absent altogether. According to the results of ultrasound examination, the volume of residual urine decreased. According to the results of the treatment, a clinical effect was noted in 29 (73%) patients, urinary incontinence – in only 6 (15%) patients.
Key words: M-anticholinergic agent, oxybutynin, overactive bladder, microcirculation.

Introduction. Urinary disorders represent one of the serious problems of modern urogynecology. A number of studies indicate an increase in the prevalence of urinary disorders in women [1, 2]. The clinical picture of urinary disorders is represented by numerous symptoms, varying in severity and nature: from urinary incontinence to acute urinary retention, which are a manifestation of a variety of diseases. The mechanism of formation of these disorders is based on the presence of obstructive urination and/or irritative disorders in patients. Overactive bladder (OAB) is a chronic symptom complex of urinary disorders. According to the European Association of Urology definition of overactive bladder and urge urinary incontinence, it is characterized by frequent urination with or without urge urinary incontinence [3, 4]. OAB occurs among 20% of patients with various urinary disorders, while urge urinary incontinence is detected in a third of these patients [5]. Women of working age from 20 to 50 years are most often affected. While not presenting an immediate threat to health, OAB,

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however, has a serious negative impact on the patient's psyche and leads to social, physiological, professional, family and sexual problems, which significantly reduces a woman's quality of life. The main urodynamic criterion for OAB is involuntary contractions of the detrusor, detected by cystometry during the filling phase of the bladder [6]. Detrusor overactivity is manifested by an increase in intravesical pressure, which causes an imperative urge to urinate. Thus, we can say that in OAB, the storage function is mainly affected [7].

Currently, there are two theories of the development of OAB: neurogenic and myogenic. According to the neurogenic theory, OAB symptoms result from increased afferent activity or decreased control of bladder storage function by the central or peripheral nervous system. This theory is confirmed by the data that, due to functional (detrusor-sphincter dyssynergia) bladder outlet obstruction, as well as some neurological diseases, the so-called C-receptors of the bladder are activated, which leads to involuntary contractions of the detrusor. The myogenic concept of OAB development suggests that the cause of detrusor hyperactivity is changes in its myocytes with disruption of intercellular connections that act as pathways. Spontaneous or induced contractions of individual myocytes can cause synchronous contraction of a significant number of muscle cells, resulting in involuntary contractions of the detrusor during the filling phase of the bladder.

Many factors are considered as reasons for the development of OAB. Some patients have idiopathic detrusor overactivity, while others develop OAB due to diseases of the central and peripheral nervous system. The development of neurogenic detrusor overactivity is a consequence of diseases of the nervous system such as Alzheimer's disease, stroke, brain tumor, multiple sclerosis and other demyelinating diseases of the nervous system, Parkinson's disease, spinal cord injury, spinal stenosis and other vertebrogenic diseases [8]. Urgent urination disorders in most cases are associated with chronic recurrent inflammatory processes, changes in hormonal levels, and innervation disorders, usually accompanied by microcirculation disorders in the bladder wall and adjacent organs [9]. A decrease in blood flow intensity leads to the development of hypoxia and disruption of metabolic homeostasis in tissues, which plays an important role in the pathogenesis of this condition

Correction of clinical manifestations of OAB in women still remains insufficiently studied and therefore ineffective in terms of therapy. Involuntary contractions of the detrusor are caused by stimulation of muscarinic M-cholinoreceptors located on the membrane of smooth muscle cells, therefore the main treatment for OAB is anticholinergic drugs. However, the anticholinergic effect of the drugs causes the development of systemic side effects of varying severity, which limits the use of these drugs in clinical practice. In the presence of obstructive urination, therapy with anticholinergic drugs is contraindicated or requires careful monitoring of the amount of residual urine. The introduction of α1-blockers into clinical practice has made it possible to develop fundamentally new methods for drug correction of urination disorders, including imperative ones [10]. The use of α-blockers has been proven to be highly effective in cases of symptoms of hyperactivity against the background of urodynamically confirmed functional bladder outlet obstruction [11]. Recent studies have shown that the dynamic

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component of bladder outlet obstruction is caused by an increase in the activity of α1-adrenergic receptors in the bladder neck and proximal urethra, which leads to spasm of the smooth muscles of these parts of the urethra [12]. Blockade of α1-adrenergic receptors is accompanied by a stereotypical detrusor response, which is expressed in its relaxation during the filling phase and an increase in the reservoir function of the bladder. As a result, significant positive changes in the functional state of the lower urinary tract are achieved, which is expressed in the disappearance of pollakiuria and normalization of the daily urination profile. Most researchers paid attention to this mechanism of action of α1-blockers. However, D. Yu. Pushkar et al. (13) suggested the effect of these drugs on the vascular system of the bladder, which was proven by research results.

Nature has created the universal M-anticholinergic drug oxybutynin, a mechanism for interconnecting biochemical processes that ensure the vital activity of the cell and the organism as a whole. This is evidenced by the discoveries of recent decades, which have shown the possibility of using M-anticholinergic inhibitors in various diseases and pathological conditions [14]. A few studies have demonstrated the effect of M-anticholinergic drugs on the vascular system of the heart, not to mention the detrusor. Currently, the issues of microcirculation and the possibility of identifying microcirculatory disorders in clinical practice are receiving increasing attention. According to the opinion of many domestic and foreign authors, the study of regional microcirculation deserves special attention in connection with its participation in the processes of repair, morphological and functional restoration of tissue and organ after various alterations and therapeutic effects [16]. Revealing microcirculatory disorders are very important for diagnosis, assessment of the severity of pathological processes in the body, control over treatment and prediction of its effectiveness. The purpose of the work was to improve the results of treatment of women with OAB and urinary incontinence by using a combination of drugs α1-adrenergic blocker and M-anticholinergic blocker oxybutynin 5 mg; study of the relationship between clinical and urodynamic manifestations of the disease, namely urge urinary incontinence and obstructive urination; study of microcirculation of the bladder mucosa before and after treatment.

Materials and methods. The study was conducted at the State institution "Republican Specialized Scientific and Practical Medical Center of Urology", Uzbekistan, Tashkent.

40 women with OAB and non-obstructive urination were examined and treated. The age of the patients ranged from 17 to 69 years (average age - 51.6 years), duration of the disease - from one year to 20 years. It should be noted that 11 (28%) patients had a history of various gynecological interventions, of which 8 (20%) were for stress urinary incontinence. Neurological disorders were detected in 28 (70%) patients: predominantly damage to the cervical and lumbar spine. A general urological examination revealed no signs of organic damage to the lower urinary tract, urethral stenosis. The patients were prescribed a combination of drugs: the α1-adrenergic blocker tamsulosin 0.4 mg at night and the M-anticholinergic blocker oxybutynin 5 mg in the morning every day for a month. Advantage. According to the

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literature, tamsulosin and oxybutynin have virtually no effect on systolic and diastolic blood pressure and heart rate. The examination included filling out a urination diary, routine urological examination methods (general urinalysis, complete blood count), urodynamic study (uroflowmetry and cystometry), ultrasound examination of the bladder with determination of residual urine.

The main method for diagnosing OAB has become a urodynamic study, which is necessary for quantitative measurement of the parameters of the storage and evacuation functions of the bladder, as well as a qualitative assessment of the results obtained. Uroflowmetry and cystometry were performed before and after treatment. Uroflowmetry was considered the most informative if there was no less than 150 and no more than 350 ml of urine in the bladder. Upon completion of the study, an automated analysis of the curve took place with printing of graphical and digital data on paper. The results obtained were assessed qualitatively and quantitatively. We paid attention to the shape of the curve, its ascending and descending segments. During quantitative assessment we determined three uroflowgram indicators: TQ – time of urination, Qmax – maximum volumetric flow rate of urine, Vcomp – volume of urine excreted. The uroflowmetry indicators obtained by E. L. Vishnevsky et al were taken as the norm. [17].

Cystometry is a study of the filling phase of the bladder, which allows you to identify the physiological and maximum volume of urination, uncoordinated, uninhibited fluctuations in detrusor pressure, and detrusor tone. It was important for us to evaluate the results of cystometric capacity and “stability” of the bladder. Cystometric capacity depends on the function of the detrusor (normal, hyperactive), the elasticity of the bladder wall, the sensory component of the nerve pathways related to the lower urinary tract. Detrusor overactivity is characterized by the presence of involuntary detrusor contractions during the filling phase of the bladder (spontaneous or provoked), which cannot be completely stopped by the patient’s volitional effort.

To study the microcirculation system of the mucous wall of the bladder of the women we examined, we used which is a modern method for assessing the state of microcirculation, based on changing the frequency characteristics of a laser beam probing tissue when it is reflected from moving blood components, primarily red blood cells. The procedure was performed using a laser blood microcirculation analyzer. Initially, we calculated the parameters of basal blood flow, i.e. The average values of changes in perfusion were calculated: the arithmetic mean value of the microcirculation index (M), standard deviation (σ) and coefficient of variation. At the second stage, the amplitude-frequency spectrum of perfusion oscillations was analyzed, since vascular tone and the state of functioning of certain perfusion control mechanisms can be assessed by the amplitudes of blood flow oscillations in specific frequency ranges.

The control group consisted of 10 women without signs of OAB, urge urinary incontinence and obstructive urination. The features of blood flow in the wall of the bladder in the control group identified during uroflowmetry were qualified by us as a physiological form of peripheral hemodynamics.

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Results and discussion. According to the treatment and examination, a clinical effect was noted by 29 (73%) patients, which was confirmed by the data of the urination diary (Table 1).

Table 1. Dynamics of clinical manifestations of the disease before and after treatment.

Symptom	Episodes before treatment	Number of episodes following treatment
Pollakiuria	17,6±4,1	9,9±1,0 p>0.001
Nocturia	5,6±0,4	2,4±0,1 p>0.001
Imperative urges	8,7±1,0	2,0±0,3 p>0.001
Feeling of incomplete emptying of the bladder	5,0±0,8	2,3±0,1 p>0.001
Weakening of the urine stream	6,1±0,4	3,1±0,3 p>0.001
Intermittent urination	5,2±0,6	3,3±0,2 p>0.001

The main side effects from the use of the drugs were dizziness, weakness and decreased blood pressure, nausea, and in some cases, flushing and palpitations. Such symptoms, as a rule, were not persistent and, over time, bothered the patients less and less. There were no refusals of treatment. According to ultrasound, before treatment the presence of residual urine in a volume of 50–270 ml
(average 105 ml) occurred in 15 (37.5%) patients; after treatment, only 6 (15%) patients had residual urine in a volume of 65–95 ml.
A decrease in the maximum volumetric flow rate of urine, an increase in the time of urination and a wave-like appearance of the uroflowgram can be a consequence of bladder outlet obstruction, a decrease in detrusor contractility, or the result of various neurogenic disorders. Visually, the uroflowgrams in all patients looked like zigzag curves, which indicates the presence of signs of hyperactivity. Quantitative uroflowmetry indicators in patients before and after treatment are presented in Table. 2.

Table 2. Uroflowmetry indicators in women before and after treatment (M±m).

Index	Before treatment	After treatment	Norm
TQ,c	49.7±0.4	21.7±0.2 p>0.001	8.77±0.66
Qmax ml/c	6,9±0,7	26,2±0,1 p>0.001	29,91±2,18
Vcom ml	67,2±3,2	155,4±1,9 p>0.001	138,11±11,63

Urodynamic disturbances, according to uroflowmetry, were expressed in a decrease in the evacuation capacity of the bladder, as indicated by an increase in urination time and a decrease in urine flow rate. The storage capacity of the bladder was also affected, as evidenced by the reduced volume of urine excreted before treatment. After treatment, urination time decreased, urination volume and maximum volumetric flow rate of urine increased. At the same time, the

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urination curve took on a less zigzag shape in all observations.

According to cystometry, in all 40 (100%) patients, the cystometric capacity was reduced and ranged from 50 to 130 ml (average 110 ml), which indicates a reduced storage function of the bladder. In all patients, we noted detrusor hyperactivity, which was manifested by the presence of involuntary detrusor contractions during the bladder filling phase (spontaneous or provoked), which could not be completely stopped by the patient's volitional effort. After treatment, the cystometric capacity increased and its values ranged from 75 to 210 ml, on average 180 ml, "stability" of the detrusor appeared in 9 (23%) patients, in the rest the number of detrusor contractions during the filling phase decreased markedly.

A decrease in the coefficient of variation, a decrease in myogenic and neurogenic tone, a shunt index, and a moderate decrease in the microcirculation efficiency index were recorded, i.e. a decrease in tissue perfusion was observed. After treatment, there was an increase in neurogenic tone in the precapillary, the shunt index and the microcirculation efficiency index, an increase in the microcirculation index and the coefficient of variation, which indicates an improvement in the condition of the bladder mucosa.

When analyzing the amplitude-frequency spectrum in the mucous membrane of the bladder wall after treatment, a statistically significant decrease in the amplitude of pulse and slow oscillations, an increase in the amplitude of fast oscillations, a significant increase in the active mechanism of microcirculation and a decrease in the indicators of the passive regulatory mechanism and vascular tension were noted, which indicates a significant decrease in stagnation blood in the venular link, i.e. about improving the state of blood flow in the wall of the bladder.

Conclusion. As the results of our study showed, the combination of the α1-adrenergic blocker tamsulosin 0.4 mg at night and the M-anticholinergic blocker oxybutynin 5 mg in the morning daily for a month is effective in the treatment of women with OAB, urge urinary incontinence and non-obstructive urination. The treatment contributed to the normalization of bladder function in the phase of both accumulation and emptying, and improvement of microcirculation in its mucosa, as evidenced by data from special research methods. According to the results of the treatment, a clinical effect was noted among 29 (73%) patients, urge urinary incontinence was observed in only 6 (15%) patients, which was confirmed by data from the urination diary.

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