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Research article

Efficacy evaluation of entomological drug Adenoprosin® usage in combined treatment of patients with lower urinary tract symptoms due to benign prostate enlargement

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BACKGROUND: Increasing the effectiveness of treatment of patients with symptoms of the lower urinary tract is one of the main problems of modern urology, which is associated both with their high prevalence and with a significant deterioration in the quality of life of patients.

AIM: The article presents the results of the usage of the entomological drug Adenoprosin® in the combined treatment of patients with lower urinary tract symptoms due to benign prostatic enlargement.

MATERIALS AND METHODS: 80 patients were treated (mean age 63.6 ± 6.4 years). At the initial phase of the study, all patients received Tamsulosin 0.4 mg once a day for 4 weeks. At the second phase, the patients were divided into two groups. Group 1 patients were prescribed a combination therapy with Adenoprosin (1 rectal suppository (150 mg) at night, for a course of 30 suppositories) and Tamsulosin (0.4 mg per day). Patients of the 2nd group continued monotherapy with Tamsulosin (0.4 mg per day). The duration of the second phase of treatment was 4 weeks.

RESULTS: The results of the study showed a more pronounced positive dynamics of clinical indicators in patients of the 1st group, who received combination therapy with Adenoprosin and Tamsulosin, compared to patients of the 2nd group. There was a more pronounced decrease in the IPSS score, an improvement in the quality of life, an increase in the urine flow rate and a decrease in the volume of residual urine. The volume of the prostate gland did not change significantly. When examined 2 weeks after the end of treatment, the positive dynamics of clinical indicators in patients of the 1st group persisted. The tolerability of the treatment was satisfactory in patients of both groups.

CONCLUSIONS: The results of the study indicate the advisability of including Adenoprosin in the combination therapy of patients with lower urinary tract symptoms due to benign enlargement of the prostate gland.

Keywords: entomotherapy; lower urinary tract symptoms; benign prostatic enlargement; benign prostatic hyperplasia; Adenoprosin®.

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ECO•VECTOR

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Научная статья

Оценка эффективности применения энтомологического препарата «Аденопросин®» в комбинированной терапии пациентов с симптомами нижних мочевых путей, обусловленных доброкачественным увеличением предстательной железы

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Актуальность. Повышение эффективности лечения пациентов с симптомами нижних мочевых путей является одной из основных проблем современной урологии, что связано как с их высокой распространенностью, так и с существенным ухудшением качества жизни пациентов.

Цель. Оценить результаты применения энтомологического препарата «Аденопросин®» в комбинированном лечении пациентов с симптомами нижних мочевых путей вследствие доброкачественного увеличения предстательной железы.

Материалы и методы. Проведено лечение 80 больных (средний возраст 63,6 ± 6,4 года). На первом этапе исследования все пациенты в течение 4 нед. получали Тамсулозин по 0,4 мг однократно в сутки. На втором этапе пациенты были разделены на две группы: в 1-й группе назначали комбинированную терапию Аденопросином — по 1 ректальной свече (150 мг) на ночь, на курс 30 свечей, и Тамсулозином — по 0,4 мг в сутки. Во 2-й группе продолжали монотерапию Тамсулозином (0,4 мг в сутки). Продолжительность второго этапа лечения 4 нед.

Результаты. Результаты исследования показали более выраженную положительную динамику клинических показателей у пациентов 1-й группы, получавших комбинированную терапию Аденопросином и Тамсулозином, по сравнению с больными 2-й группы. Отмечено более выраженное снижение суммы баллов по шкале IPSS, улучшение качества жизни, увеличение скорости потока мочи и уменьшение объема остаточной мочи. Объем предстательной железы достоверно не изменялся. При обследовании через 2 нед. после окончания лечения положительная динамика клинических показателей в 1-й группе сохранялась. Переносимость лечения была удовлетворительной у пациентов обеих групп.

Выводы. Результаты проведенного исследования указывают на целесообразность включения Аденопросина в комбинированную терапию пациентов с симптомами нижних мочевых путей вследствие доброкачественного увеличения предстательной железы.

Ключевые слова: энтомотерапия; симптомы нижних мочевых путей; доброкачественное увеличение предстательной железы; доброкачественная гиперплазия предстательной железы; Аденопросин®.

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ЭКО•ВЕКТОР

INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common diseases in older men [1]. The significance of BPH is associated not only with its high prevalence but also with a significant decrease in the quality of life of patients and the risk of severe complications [2, 3]. BPH can be morphological or clinical. The latter is manifested by various urinary disorders, which collectively referred to "lower urinary tract symptoms (LUTS)." The frequency of LUTS is high; according to an epidemiological study conducted in the Northwestern Federal District, 67.7% of adult men report LUTS, and the number of such respondents increases with age [4]. In this regard, experts from the European Association of Urology in recent years recommend focusing on the severity of LUTS when choosing treatment and not only on the presence of prostate enlargement, as was previously accepted [5]. Treatment of patients with urination disorders caused by benign prostate enlargement can be conservative or surgical. In recent decades, the medical therapy of BPH has progressed significantly, which has enabled successful long-term drug treatment of several patients and has led to a decrease in the number of surgical interventions [6]. The main groups of drugs for the treatment of BPH include 5-alpha-reductase inhibitors, alpha-blockers, M-cholinoblockers, and type 5 phosphodiesterase inhibitors. Combination therapy with co-administration of alpha-blockers and 5-alpha-reductase inhibitors, alpha-blockers and M-cholinoblockers, and alpha-blockers and type 5 phosphodiesterase inhibitors has become widespread [7–9]. Despite the high clinical efficacy of drug treatment, adverse events are often recorded, such as hypotension, ejaculatory dysfunction, xerostomia, and intraoperative iris flaccidity syndrome.

An example of conservative therapy is herbal medicine, which is characterized with good tolerability, as side effects of treatment are rare and usually mild [10]. In many countries, patients with LUTS prefer herbal drugs. In some European countries, particularly Italy, Austria, and Germany, phytopreparations are prescribed more often than alpha-blockers or 5-alpha-reductase inhibitors. Numerous studies have confirmed the efficiency of herbal medicines, which led to the inclusion of herbal medicines in the clinical guidelines of the European Association of Urology for the treatment of non-neurogenic LUTS in men to improve their quality of life [11]. Along with phytotherapy, the use of drugs of biological origin, considered as an alternative to chemical synthesis drugs, tended to increase. The efficacy and safety of animal preparations are comparable with those of herbal drugs [12].

In recent years, entomotherapy has received increased attention, that is, the use of insect-based medicines, which is a new field of conservative treatment of urological patients. It is noteworthy that interest in the study of insects accompanied humanity throughout its development. The use of insects for the manufacture of drugs has been known since ancient Greece, where "tincture of bedbugs" was used in the treatment of difficulty in urination and bleeding. However, scientific research in this field started only in the XVII century. The Italian biologist and physician Marcello Malpighi (1628–1694) and the Dutch scientist Jan Swammerdam (1637–1680) had made great contribution to the development of entomology [13]. Their works formed the basis for the development of medical entomology, which arose at the intersection of sciences such as biology and medicine, and led to the creation of entomotherapy, which is successfully used nowadays in various fields of medicine, including urology.

The currently used entomological drugs have pronounced antimicrobial and cytoprotective effects and bind free radicals, with minimal or absent side reactions [14]. One of these drugs is Adenoprosin®, which has been used in urological practice since 2011 and has been successful in the treatment of BPH and chronic prostatitis. The drug preparation is based on the biomass of gypsy moth larvae *Lymantria dispar*, which has a specific antioxidant activity, inhibiting the oxidation of low-density lipoproteins and reducing the content of NO radicals [15]. The drug reduces capillary permeability, reduces swelling, and improves microcirculation in the prostate gland. In addition, Adenoprosin reduces the production of proinflammatory cytokines, namely, interleukins-6 and -8 (IL-6 and IL-8), and inhibits the synthesis of endothelial vascular growth factor (VEGF) [16].

Studies have confirmed the efficiency of Adenoprosin. Thus, in 2011, Ghicavii et al. used Adenoprosin to treat 85 patients with BPH. The authors noted clinical improvement, which was manifested as a decrease in the severity of LUTS and an improvement in erectile function. According to the researchers, such a double clinical effect is caused by the positive effect of Adenoprosin on the hemodynamics of pelvic organs [17]. Saidulloev et al. [18] reported normalization of the structure and echogenicity of the prostate gland and ejaculate parameters and a decrease in the severity of LUTS in 64 patients with chronic prostatitis who took Adenoprosin. The efficiency of Adenoprosin has also been confirmed by other researchers. Moreover, several aspects of the clinical use of this drug remain unclear, particularly the efficiency of Adenoprosin in combination with other drugs for the treatment of BPH.

This study aimed to evaluate the efficacy and tolerability of Adenoprosin in combination with the alpha-blocker tamsulosin in patients with mild-to-moderate LUTS associated with benign prostate enlargement.

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MATERIALS AND METHODS

Based on the clinic of urology and the consultative and diagnostic center of the First Pavlov Saint Petersburg State Medical University, 80 men aged 57–70 years (mean age, 63.6 ± 6.4 years) with LUTS associated with benign prostate enlargement were examined and treated. All patients complained of dysuric phenomena, including nocturia (2–6 urination per night).

The inclusion criteria were as follows: age 50 years or older, complaints of urinary disorders, >10 points on the International Prostate Symptom Score (IPSS) scale, prostate-specific antigen level in the serum not more than 3.0 ng/mL, prostate level during transrectal ultrasound study (US) >30 cm^3, maximum volumetric urination rate of 6–13 mL/s with an urination volume of at least 130 mL, and residual urine volume (RUV)of 50–150 mL. The study included men who had not received conservative therapy for LUTS within the last month. All patients signed an informed consent to participate in the study.

The exclusion criteria were as follows: exacerbation of urinary tract infections, impaired renal function, neurogenic nature of urination disorders, history of malignant neoplasms of the kidneys, urinary tract and prostate gland, indications for surgical treatment of BPH, and comorbidities complicating the study.

At stage 1 (preliminary) of the study, all 80 patients were treated within 4 weeks with tamsulosin 0.4 mg once a day. Fourteen days after the start of conservative therapy, treatment tolerability and the need for its correction were assessed. Six patients complained of hypotension, which was resolved after consultation with a cardiologist and correction of antihypertensive therapy. Ejaculatory dysfunction occurred in three patients and was not significant, as these men lacked an active sexual life; therefore, alpha-blocker therapy was continued.

At stage 2 (main), patients were distributed into two groups of 40 people by random number method using an automated random number generator. In group 1 (n = 40), patients received the combination therapy with tamsulosin (0.4 mg once a day) and Adenoprosin® (rectal suppositories containing 150 mg of the active substance, once at night) for 30 days. Three days after the start of the combination therapy, one patient complained of a burning sensation and itching in the anus; therefore, the combination therapy was canceled, and the patient was excluded from the study (n = 39). In group 2 (n = 40), patients continued monotherapy with tamsulosin (0.4 mg once a day). Two weeks after the end of treatment, group 1 underwent a control examination.

The patients underwent a comprehensive urological examination, which included an assessment of symptoms scored in points on the IPSS scale, assessment of the quality of life (QoL), laboratory tests (biochemical blood test, blood test for a prostate-specific antigen, and general urinalysis), and instrumental studies (uroflowmetry, transrectal US of the prostate gland, US of the bladder with determination of the RUV, and US of the kidneys). Control examinations were performed before treatment and 4 and 6 weeks after the start of treatment. Tolerability of therapy was assessed by the frequency and severity of local and/or systemic adverse events.

All data obtained were entered into a special research card. The calculation and statistical analysis of the study results was performed using the Statistica 10.0 program. Quantitative variables were described by statistical methods, namely, number of valid cases, arithmetic mean (M), and standard deviation from the arithmetic mean (σ). Qualitative variables were described by absolute and relative frequencies (percentages). Differences were considered significant at the error level p lower than 0.05. We used unpaired Student's t-test and non-parametric Mann–Whitney tests to assess the dynamics of changes in data expressed in quantitative terms.

RESULTS AND DISCUSSION

Table 1 presents the results of the preliminary and main stages of the study. At stage 1, all 80 patients were treated with the alpha-blocker tamsulosin, which was accompanied by improvement in the main clinical indicators of the disease course.

During the main stage of the study, the efficiency of the combination therapy with tamsulosin and Adenoprosin (group 1, n = 39) was compared with tamsulosin monotherapy (group 2, n = 40). More pronounced improvement after 4 weeks from the start of treatment was noted in group 1. After the main stage of treatment, the average urinary flow rate in group 1 increased by 15.7% compared with the baseline rate and only by 5% in group 2 ($p < 0.05$). The RUV decreased in groups 1 and 2 by 7.1% and 4.2%, the total score on the IPSS scale by 19.9% and 6.1% ($p < 0.05$), and QoL indicator by 68.4% and 45.4% ($p < 0.05$) respectively. Moreover, no significant changes were noted in the volume of the prostate gland in both groups compared with the initial values. A remarkable decrease in the intensity of nocturia was noted in group 1 compared with group 2 by an average of 29% and 10%, respectively.

At two weeks after the main stage of the study, group 1 underwent a control examination (Table 2). None of the studied indicators showed negative dynamics.

The results indicated the clinical efficacy of both tamsulosin monotherapy and the combination of tamsulosin and Adenoprosin. In addition, the combination therapy led to a more pronounced improvement in the clinical indicators of BPH. The tolerability to Adenoprosin was satisfactory, while only one patient had adverse effects (i.e., burning and itching in the anus).

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Table 1. The main clinical indicators of patients with BPH, obtained during the preliminary and main stages of the study, $M \pm \sigma$

Таблица 1. Основные клинические показатели пациентов с доброкачественной гиперплазией предстательной железы, полученные на предварительном и основном этапах исследования, $M \pm \sigma$

Indicator	Preliminary stage		Main stage, after 4 weeks of treatment	
	Before treatment (n = 80)	After 4 weeks (n = 80)	Group 1 (n = 39)	Group 2 (n = 40)
Q_{max}, ml/s	8.7 ± 1.1	11.9 ± 0.8*	14.1 ± 0.5*	12.5 ± 0.8*
Residual urine volume, mL	77.3 ± 12.3	48.3 ± 11.3*	44.8 ± 5.7*	46.1 ± 10.3*
IPSS, points	17.7 ± 1.3	13.3 ± 1.2*	10.6 ± 1.1*	12.5 ± 1.5*
QoL, points	4.1 ± 1.4	3.2 ± 1.3*	1.9 ± 0.2*	2.2 ± 0.1*
Prostate volume, cm^3	56.5 ± 12.3	55.8 ± 12.4	54.3 ± 12.7	54.9 ± 12.3

Note. * The difference between the indicators before and after treatment was significant ($p < 0.05$).

Table 2. The main clinical indicators of patients of the 1st group during and after treatment, $M \pm \sigma$

Таблица 2. Основные клинические показатели пациентов в 1-й группе во время и после лечения, $M \pm \sigma$

Indicator	After 4 weeks of treatment (n = 39)	2 weeks after the treatment (n = 39)
Q_{max}, ml/s	14.1 ± 0.5	14.1 ± 0.8
Residual urine volume, mL	44.8 ± 5.7	44.7 ± 10.3
IPSS, points	10.6 ± 1.1	10.7 ± 1.5
QoL, points	1.9 ± 0.2	1.9 ± 0.1
Prostate volume, cm^3	54.3 ± 12.7	54.5 ± 12.3
Frequency of nocturnal urination	1.5	1.5

Note. The difference between the indicators before and after treatment was insignificant ($p < 0,05$).

To date, undoubtedly, the major cause of BPH is an increase in the proliferation of prostate cells due to an increase in the concentration of dihydrotestosterone. The role of inflammation in BPH development has also been proven, i.e., inflammatory infiltrates produce cytokines (IL-6, IL-8, and IL-21) and fibroblast growth factor, which leads to increased fibroblast proliferation and disruption of the metabolic processes in the prostate gland [19]. Histological studies of prostate tissues obtained from biopsies in patients with BPH detected an inflammatory process in 80% of the cases [20]. Prostatitis accelerates the growth of hyperplastic prostate tissue and increases the severity of the clinical symptoms [21]. The above finding explains the efficiency of Adenoprosin®, which has anti-inflammatory, immunomodulatory, and antioxidant properties in patients with LUTS associated with benign prostate enlargement. Adenoprosin inhibits the main links of the arachidonic acid cascade, leading to a decrease in vascular wall permeability. Over the past few years, several studies have indicated the safety and high efficiency of Adenoprosin®. Thus, Demidko et al. [22] analyzed seven studies that investigated the effect of Adenoprosin and reported its effectiveness in the treatment of LUTS caused by benign prostate enlargement, its inflammation, and their combination. Medvedev and Efremov [23] proved the efficiency of Adenoprosin in the treatment of chronic bacterial prostatitis. The authors noted not only a decrease in the clinical manifestations but also a decrease in the number of leukocytes in prostate secretions, an improvement in drainage of the prostate gland, a decrease in parenchymal edema, and a decrease in prostate gland congestion. Kuzmenko et al. [24] reported a decrease in the severity of dysuric phenomena and pain syndrome in 30 patients with BPH and chronic prostatitis while taking Adenoprosin® and fluoroquinolones, compared with patients taking standard antibiotic therapy. The authors attributed the positive effect of the entomological drug to its anti-inflammatory action.

CONCLUSIONS

The results of this study showed the efficiency and good tolerability to the entomological drug Adenoprosin® in the combination therapy for patients with mild-to-moderate LUTS associated with benign prostate hyperplasia. Thus, it can be recommended for wide clinical application.

ADDITIONAL INFORMATION

Author contributions. All authors confirm that their authorship complies with ICMJE criteria. All authors have made a significant contribution to the development of the concept, research, and preparation of the article. They have read and approved the final version before its publication.

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

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