Application of the Entomological Drug Adenoprosin in the Treatment of Patients with Benign Prostatic Hyperplasia and Chronic Prostatitis

A.V. Kuzmenko, V.V. Kuzmenko, T.A. Gyaurgiev

Urology Department, Voronezh State Medical University n.a. N.N. Burdenko, Voronezh, Russia

Abstract

Introduction and Objectives. Benign prostatic hyperplasia (BPH) and chronic prostatitis (CP) are usually parts of the symptom complex that manifests age-related health changes in men. The combination of BPH with CP raises many questions in choosing the right treatment tactics. Currently, new medicines have been developed and widely used – entomological preparations, which are biologically active substances with antioxidant and anti-radical properties. The purpose of our study is to study the effectiveness of the entomological drug Adenoprosin in the complex therapy of patients with BPH and chronic prostatitis.

Materials and Methods. The study included 60 patients with BPH and CP. Patients were randomized into two groups of 30 people. In the comparison group, we prescribed a therapy with alpha-blockers and fluoroquinolones. In the main group, patients were prescribed similar traditional therapy with alpha-blockers and fluoroquinolones, but in combination with Adenoprosin once a day for three months. The results were evaluated before the treatment (Visit 1), after four weeks (Visit 2) and three months (Visit 3) of therapy. We determined the frequency of urination, the number of night urinations, the average score on the IPSS, QOL, NIH-CPSI scales, the maximum urine flow rate (Q max), prostate volume and residual urine volume.

Results. By the second visit, despite the absence of significant differences ($p>0.05$), the main group showed a more pronounced positive dynamics of changes in the results of most studies. According to data obtained on visit 3, the results in the comparison group did not significantly changed since the previous visit. In the main group, there was a significant decrease in the number of day and night urinations, an increase in the urine flow rate and the average score on the NICH-CPSI, IPSS and QOL scales, and a decrease in the prostate volume and the volume of residual urine. The results, obtained in the main group, differed significantly ($p<0.05$) from the indicators in the comparison group.

Conclusions. Thus, the entomological drug Adenoprosin, taking into account its anti-inflammatory, antioxidant activity and antiproliferative effect against prostate hyperplasia cells, can become a new direction in the complex therapy of patients with BPH and CP. However, to confirm the results, obtained at this stage, and to study in more detail the mechanisms of therapeutic effect of this group of drugs, it is necessary to conduct comprehensive placebo-controlled clinical studies.

Keywords: Adenoprosin, benign prostatic hyperplasia, chronic prostatitis, entomological drugs.

Correspondence to: Kuzmenko Andrey Vladimirovich, MD, head of the Urology Department Voronezh State Medical University n.a. N.N. Burdenko;
tel. 8 903 653 05 94;
e-mail: kuzmenkoav09@yandex.ru.

Introduction and Objectives

Benign prostatic hyperplasia (BPH) and chronic prostatitis (CP) are widespread and are among the most significant urological diseases [1-5].

Under the age of 60, BPH diagnoses in more than 42% of men. By the age of 90, the disease detects in almost 90%. More than 30% of such patients undergo surgical treatment at least once during their life [6-9].

Chronic inflammation of the prostate is one of the most frequently recurring urological diseases and is usually poorly treatable. According to the National Institute of Health, about 25% of men suffering from diseases of the urinary system have symptoms of prostatitis, which is more than 9% of the male population [3-5].

Prostate hyperplasia often occurs on the background of inflammatory changes, which are usually focal and limited to the paraurethral zone. Data from morphological studies conducted in men with BPH in 96.7% indicate the presence of signs of chronic inflammation of various degrees of severity in the tissues of the prostate [11]. According to the results of some studies on this problem, 57.2% of men with CP had BPH, and 38.7% of patients with BPH had CP [6-9, 11].

The significance of BPH and CP determines not only by their prevalence, but also by a significant decrease in the quality of life of this category of patients. In addition, you should remember about the high frequency of complications, such as acute urinary retention, damage to the upper urinary tract, erectile dysfunction [12, 13].

The causes of comorbidity of BPH and CP include microcirculation disorders and venous stasis, congestion in the prostate and compression of the acinus ducts. Certain anatomical features, uncontrolled and/or irregular sexual life, sedentary passive lifestyle, chronic intoxication, and urethrogenic infections can lead to stagnant processes in the pelvis and cause the development of inflammatory changes in the prostate tissue [14, 15].

Concomitant CP negatively affects the clinical course of BPH. Inflammatory changes in the prostate can affect both irritative and obstructive symptoms. Underestimating the symptoms of prostatitis can cause poor effectiveness of conservative treatment and lead to an increase in the number of complications after surgical treatment [16-18].

Currently, there is a wide range of treatment methods, ranging from conservative drug therapy to surgical interventions. The first line of therapy for patients with BPH includes the use of alpha-blockers and 5-alpha-reductase inhibitors. Treatment of patients with CP mainly carries out using antibacterial and anti-inflammatory agents. In addition, actively used herbal remedies and physical therapy [1, 2].

However, the combination of BPH with CP raises many questions in choosing the right treatment tactics. The predominance of irritative symptoms, the lack of a stable satisfactory effect from taking alpha-blockers, and frequent exacerbations of CP make it necessary to use additional methods in the treatment of such patients [13, 19-21].

Recently, a new group of entomological preparations, which are biologically active substances with anti-inflammatory and antioxidant properties obtained from the biomass of certain insects, has been widely used [22, 23].

Adenoprosin is a new entomological drug that obtains from the larvae of Lymantria dispar using modern biotechnologies. Pre-clinical studies have shown that the drug has anti-inflammatory, antioxidant, angioprotective, immunomodulatory properties, which allows using it as an adjunct in the treatment of patients with BPH and CP [24, 25].

The purpose of our study is to study the effectiveness of the entomological drug Adenoprosin in the complex therapy of patients with BPH and chronic prostatitis.

Materials and Methods

The study included 60 patients with BPH and CP. The diagnosis was made according to generally accepted criteria (NIH recommendations, 1995) [26].

Patients met the following inclusion criteria of the study: the total score from 8 to 19 points on the IPSS scale and more than 14 points on the NIH-CPSI scale. The volume of residual urine – from 30 to 100 ml, prostate volume of more than 30 cm^3, a PSA – up to 4 ng/ml, no concomitant drug therapy, signed informed consent for participation in the study.

The criteria for non-inclusion were bladder and ureter stones, hematuria, prostate or bladder cancer, allergic reactions to medications used, pelvic surgery, urinary tract infections, neurogenic bladder dysfunction, congenital abnormalities of the genitourinary system, oncological and severe cardiovascular diseases, diabetes mellitus, hypogonadism.

Patients were randomized into two groups of 30 people. In the main group (MG), patients were prescribed similar traditional therapy with alpha-blockers and fluoroquinolones, but in combination with Adenoprosin once a day for three months.

In the comparison group (CG), we prescribed a therapy with alpha-blockers (tamsulosin 0.4 mg once a day) and fluoroquinolones (levofloxacin 500 mg once a day for four weeks).

In the main group (MG), patients were prescribed similar therapy with alpha-blockers and fluoroquinolones, but in combination with Adenoprosin once a day for three months.

The effectiveness of treatment was evaluated before the treatment (Visit 1), four weeks (Visit 2) and three months (Visit 3) after the start of therapy. We determined the frequency of urination, the number of night urinations, the average score on the IPSS, QOL, NIH-CPSI scales, the maximum urine flow rate (Q max), prostate volume and residual urine volume.

We performed statistical processing of the results using MS Excel 11.0 from the standard MS Office 2013 package, as well as IBM SPSS Statistics 21.0 software. For testing statistical hypotheses we used the methods of parametric (student's t-test) statistics. In all of the cases, a p value < 0.05 was considered significant.

Results

The comparative characteristics of the research results, obtained during three months in both groups, are presented in the table.

As can be seen from the data obtained (see the table), initially the groups were homogeneous, and there were no significant differences in the studied indicators. By the second visit, patients in both groups had a decrease in dysuric symptoms, an increase in Qmax, which led to an increase in the average score on the IPSS and QOL scales. In addition, according to ultrasound data, there was a decrease in the volume of residual urine in both groups. Despite the absence of significant differences (p>0.05), the main group showed a more pronounced positive dynamics of changes in most of the studied indicators, especially prostate volume.

After three months of therapy on visit 3, the results in the comparison group did not significantly change from the previous session. The results obtained in the main group differed significantly (p<0.05) from the indicators in the comparison group (Pic 1A, 1B)

In the main group by this time, the number of day and night urinations were 20.3% and 31.6% less, respectively. The result on the NIH-CPSI scale was lower by an average of 4.7 points; on the IPSS scale –by 4.2 points, and the quality of life according to the QOL scale improved by 1.1 points (fig. 1A). These subjective changes in the condition of patients are confirmed by objective data: the maximum flow rate of urine in the main group was 21.6% higher, the prostate volume was 12.3% lower, and the volume of residual urine was 18.5% lower (fig. 1B).

Discussion

Insects have long been known as a source of medicine. The study of insect biochemistry allowed us to explain that numerous peptides, hormones, pheromones and other biologically active substances, produced in

Table. Comparative characteristics of research results, obtained over three months in both groups.

Visits	Visit 1 (before treatment)		Visit 2 (four weeks)		Visit 3 (three months)	
Groups	CG	MG	CG	MG	CG	MG
Frequency of urination (number)	13.8±2.1	13.7±2.2	7.2±1.3	7.0±1.1	6.9±1.1	5.5±1.2*
Number of night urinations	4.2±1.4	4.3±1.5	2.0±0.9	1.9±0.9	1.9±1.0	1.3±1.0*
IPSS (score)	18.6±1.2	18.5±1.2	14.1±1.2	14.0±1.1	14.0±1.0	9.8±1.1*
QOL (score)	2.0±0.9	2.1±0.9	3.0±1.1	3.2±0.9	3.2±1.0	4.3±0.7*
NIH-CPSI (score)	27.1±2.0	27.2±2.2	18.4±2.5	18.1±2.1	17.1±2.0	12.4±2.6*
Qmax (ml/sec)	7.8±1.7	7.9±1.8	10.8±2.2	11.0±2.4	10.9±1.9	13.9±2.3*
Prostate volume (sm^3)	61.1±10.7	60.7±10.4	54.2±10.6	51.7±12.1	54.6±10.8	47.9±10.4*
Residual urine volume (sm3)	53.4±12.8	53.9±12.2	26.2±9.1	25.4±8.3	23.3±8.2	19.0±7.2*

*Note: * - Significant differences with the comparison group (p<0.05)*

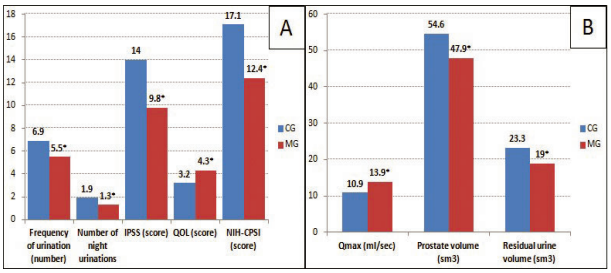


Figure 1 (A, B). Results of examination in two groups after three months of therapy
*Note: * - Significant differences with the comparison group (p<0.05)*

small quantities, have a number of beneficial effects on the human body. One of the representatives of this group of substances is drug Adenoprosin.

L. Olariu et al. identified an antioxidant effect associated with a decrease in intracellular hydrogen peroxide in prostate hyperplasia cells, as well as a significant decrease in the activity of extracellular interleukin-6 and interleukin-8, which confirms the presence of an anti-inflammatory effect of Adenoprosin [22].

Ghicavii V. et al. on the results of their study concluded that Adenoprosin could reduce fibrotic changes in the prostate and its volume. This remedy can quickly and effectively affect the elimination of symptoms of the disease and improve urodynamic indicators in the first three or four weeks of treatment. According to the authors, the decrease in the volume of the prostate gland occurs by both reducing paraprostatic edema and venous retention in the prostate tissue, and by affecting the vascular phase of capillary permeability during inflammation [24].

In their study, I. Dumbraveanu et al. appointed by Adenoprosin men with chronic prostatitis and, arising on its background, erectile dysfunction. According to the results of the study, a significant reduction in the symptoms of chronic prostatitis was observed in patients [23, 25].

The results of our research are consistent with the data presented in the literature. Application of Adenoprosin showed a decrease in the severity of lower urinary tract symptoms and symptoms of chronic prostatitis, an increase in the maximum urine flow rate, a decrease in the prostate volume and the residual urine volume after four weeks of taking the drug. However, statistically significant (p<0.05) differences with the comparison group for all studied parameters were observed after three months of therapy.

The results obtained may be due not only to the anti-inflammatory effect that reduces paraprostatic edema and venous stasis in the prostate tissue, but also to the effect on the vascular phase of capillary permeability during inflammation. Adenoprosin can also protect cells from apoptosis under inflammatory conditions, while causing the exact opposite effect in hyperplastic cells in the absence of inflammation, inducing apoptosis of prostate cells. The antiproliferative effect is also indicated by the study of L. Olariu et al. reducing the formation of prostate hyperplasia cell colonies [22]. However, these pathogenetic mechanisms require further study and confirmation.

Conclusions

Thus, entomological drugs, in particular Adenoprosin, taking into account their anti-inflammatory, antioxidant activity and antiproliferative effect against prostate hyperplasia cells, can become a new direction in the complex therapy of patients with BPH and CP. However, to confirm the results obtained at this stage and to study in more detail the mechanisms of therapeutic effect of this group of drugs, it is necessary to conduct comprehensive placebo-controlled clinical studies.

References

1. Urology. Russian clinical guidelines. Under the editorship of Yu. G. Alyaev, P. V. Glybochko, D. Yu. Pushkar. M.: GEOTAR-Media; 2018. 480s. Russian (Урология. Российские клинические рекомендации. Под ред. Ю.Г. Аляева, П.В. Глыбочко, Д.Ю. Пушкаря. М.: ГЭОТАР-Медиа; 2018. 480с.)
2. Gravas S., Cornu J.N, Drake M.J et al. *EAU guidelines on the management of non-neurogenic male lower urinary tract symptoms (LUTS), incl. benign prostatic obstruction (BPO).* 2018. Available at: http://uroweb.org/guideline/treatment-of-non-neurogenic male-luts/ Accessed 5 May 2019
3. Schaeffer AJ. *Classification (Traditional and National Institutes of Health) and Demographics of Prostatitis* / Urology. 2002 Dec;60(6 Suppl):5-6; discussion 6-7. doi: 10.1016/s0090-4295(02)02292-6.
4. Nickel J. Prostatitis. CUA Guidelines. *Canadian Urol. Assoc.* J., 2011; 5 (5): 306-15. https://www.ncbi.nlm.nih.gov/pubmed/22031609
5. Rees J., Abrahams M., Doble A., *Cooper A. and the Prostatitis Expert Reference Group (PERG). Diagnosis and treatment of chronic bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome: a consensus guideline.* BJU Int., 2015; 116: 509-525. https://doi:10.1111/bju.13101
6. Gupta N, Rogers T, Holland B, Helo S, Dynda D, McVary K.T. *Three-year treatment outcomes of water vapor thermal therapy compared to doxazosin, finasteride and combination drug therapy in men with benign prostatic hyperplasia: cohort data from the MTOPS Trial.* J Urol. 2018 Aug;200(2):405-413. doi: 10.1016/j.juro.2018.02.3088.

7. Roehrborn C.G, Barkin J, Tubaro A, Emberton M, Wilson T.H, Brotherton B.J, Castro R.P. *Influence of baseline variables on changes in International Prostate Symptom Score after combined therapy with dutasteride plus tamsulosin or either monotherapy in patients with benign prostatic hyperplasia and lower urinary tract symptoms: 4-year results of the CombAT study.* BJU Int. 2014 Apr;113(4):623-35. doi: 10.1111/bju.12500.
8. Roehrborn C.G, Barkin J, Siami P, Tubaro A, Wilson T.H, Morrill B.B, Gagnier R.P. *Clinical outcomes after combined therapy with dutasteride plus tamsulosin or either monotherapy in men with benign prostatic hyperplasia (BPH) by baseline characteristics: 4-year results from the randomized, double-blind Combination of Avodart and Tamsulosin (CombAT) trial.* BJU Int. 2011 Mar;107(6):946-54. doi: 10.1111/j.1464-410X.2011.10124.x.
9. Roehrborn, C.G., Oyarzabal Perez I., Roos E.P., Calomfirescu N., Brotherton B., Wang F., Palacios J.M., Vasylyev A., Manyak M.J. *Efficacy and safety of a fixed-dose combination of dutasteride and tamsulosin treatment (Duodart) compared with watchful waiting with nitiation of tamsulosin therapy if symptoms do not improve, both provided with lifestyle advice, in the management of treatment-naive men with moderately symptomatic benign prostatic hyperplasia: 2-year CONDUCT study results.* BJU Int. 2015;7. doi: 10.1111/bju.13033
10. Kudryavtsev Yu. V., Sivkov A.V. *Morphological changes in prostate tissue in benign hyperplasia.* Experimental and clinical urology. 2010;1:18-22
11. Bartoletti R., Cai T, Mondaini N., Dinelli N., Pinzi N., Pavone C. et al. *Prevalence, incidence estimation, risk factors and characterization of chronic prostatitis/chronic pelvic pain syndrome in urological hospital outpatients in Italy: results of a multi-center case-control observational study.* J. Urol., 2007; 178: 11-15. https://www.ncbi.nlm.nih.gov/pubmed/17937946
12. Krsmanovic A., Tripp D., Nickel J. et al. *Psychosocial mechanisms of the pain and quality of life relationship for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).* Canadian Urological Association Journal, 2014; 8 (11-12): 403-408. https:// doi:10.5489/cuaj.2179
13. Kuzmenko A.V., Kuzmenko V. V., Gyaurgiev T. A., Barannikov I. I. *Chronobiological status of patients with chronic prostatitis on the background of prostate adenoma.* System analysis and management in biomedical systems. 2017;16(3):513-316.
14. Huang T., Li W., Peng B. *Correlation of inflammatory mediators in prostatic secretion with chronic prostatitis and chronic pelvic pain syndrome.* Andrologia, 2017; e12860. https://doi.org/10.1111/and12860
15. Hu C., Yang H., Zhao Y. et al. **The role of inflammatory cytokines and ERK1/2 signaling in chronic prostatitis/chronic pelvic pain syndrome with related mental health disorders.** Sci. Rep., 2016; 6: 28608. https://www.ncbi.nlm.nih.gov/pubmed/27334333
16. Kuzmenko A.V., Kuzmenko V. V., Gyaurgiev T. A. *Combined drug therapy of patients with BPH.* Urology. 2018; 1:101-105.
17. Kuzmenko A.V., Kuzmenko V. V., Gyaurgiev T. A. *Efficacy of fesoterodine in patients after transurethral resection of the prostate.* Urology. 2019;1:52-55.
18. Kuzmenko A.V., Kuzmenko V. V., Giaurgiev T. A. *Effectiveness of macrolides in the treatment of patients with urogenital infections.* RMJ. 2019; 27 (10):46-49.
19. Alyaev Yu. G., Gadzhieva Z. K., Rapoport L. M., Kazilov Yu. B. *Medical treatment of lower urinary tract symptoms in men. The role of uroselectivity in drug selection.* Andrology and genital surgery. -2014;1:6-14.
20. Gadzhieva Z. K., Kazilov Yu. B. *New possibilities of treatment of combined symptoms of the lower urinary tract in patients with benign prostatic hyperplasia - prerequisites and advantages.* Urology. 2017;1:95-102.
21. Neymark A. I., Neymark B. A., Torbik D. V. *Tactics of managing a patient with benign prostatic hyperplasia with a large volume of it.* Bulletin of medical science. 2017;1 (5):44-53.
22. L. Olariu et al. *Entomological complex with pro-apoptotic and antiproliferative effect on prostatic dysplasia cells,* EUROINVENT Cat., Timisoara,2017.
23. Dumbraveanu I., Banov P., Arian I., Tanase A. *Use of entomological drugs in the complex treatment of patients with chronic prostatitis and erectile dysfunction.* Moldovan Journal of Health Sciences 14(4),2017
24. Ghicavii V., Tanase A., Ceban E., Dumbraveanu I., Ciuhrii V. *New Direction in the Treatment of Benign Prostate Hyperplasia Using Adenoprosin*: Biologically' Active Entomological Medicine. UROLOGY, Vol. 78 ,2011
25. Dumbraveanu I. et al. *Adenoprosin in the treatment of prostate diseases.* Arta Medica. Revista medícala ptiintifi co-practică, 2015; 4 (57): 101-104.
26. National Institutes of Health Summary Statement. National Institutes of Health / National Institute of Diabetes and Digestive and Kidney Diseases workshop on chronic prostatitis. Executive Summary, Bethesda MD, December, 1995.

Author information:

Kuzmenko A.V. – MD, professor, Head of the Urology Department of Voronezh State Medical University named after N.N. Burdenko, Voronezh, Russia; e-mail: Kuzmenkoav09@yandex.ru

Kuzmenko V.V. – MD, professor at the of Urology Department of Voronezh State Medical University named after N.N. Burdenko, Voronezh, Russia; e-mail: kuzmenkovv2003@mail.ru

Gyaurgiev T.A. – Ph.D., associate professor at the of Urology Department of Voronezh State Medical University named after N.N. Burdenko, Voronezh, Russia; e-mail:tima001100@mail.ru