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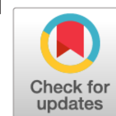
Chronobiological approach to the treatment of patients with benign prostate hyperplasia and chronic prostatitis: results of a morphological examination



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MATERIALS AND METHODS: 60 patients with benign prostatic hyperplasia (BPH) and category II chronic prostatitis (NIH, 1995) were examined. The average age of the patients was 60.5 ± 5.5 years. The patients were divided into two groups of 30 people each. The comparison group (GC) included patients who received standard therapy with drugs from the group of alpha-blockers and fluoroquinolones. The main group (MG) consisted of patients who received standard therapy in combination with physiotherapy sessions with the device "SMART-PROST", which were carried out in the acrophase of the chronorhythm. After the end of the course of therapy all patients underwent transurethral resection of the prostate, after which a morphological and morphometric (immunohistochemical) study of the obtained material was carried out.
RESULTS: According to the results of the morphological and morphometric examination of the histological material in patients of the CG and MG, statistically significant differences were revealed in all the studied parameters, which testify to the persistence of signs of the inflammatory process in the CG, while in the MG, the severity of inflammation was significantly lower.
CONCLUSION: According to the results of the study, personalized complex therapy of patients with benign prostatic hyperplasia in combination with chronic prostatitis using a combined physiotherapeutic effect of the SMART-PROST device, taking into account the individual chronobiological characteristics of patients, allows to more effectively arrest the inflammatory process in the prostate tissue, which can lead to a decrease in the number of postoperative complications. However, the last statement requires further more detailed study.

Keywords: chronic bacterial prostatitis; benign prostatic hyperplasia; BPH; TUR of the prostatae; chronotherapy; physiotherapy with the SMART-PROST device; morphometry; immunohistochemistry.

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Хронобиологический подход к лечению больных доброкачественной гиперплазией предстательной железы и хроническим простатитом: результаты морфологического исследования

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Материалы и методы. Обследованы 60 пациентов с доброкачественной гиперплазией предстательной железы (ДГПЖ) и хроническим простатитом категории II (NIH, 1995). Средний возраст больных составил 60,5 ± 5,5 года. Пациенты были распределены в две группы по 30 человек. В группу сравнения (ГС) включены пациенты, которым проводили стандартную терапию препаратами из группы альфа-блокаторов и фторхинолонов. В основную группу (ОГ) входили пациенты, получавшие стандартную терапию в сочетании с сеансами физиотерапии аппаратом «Смарт-Прост», проводившиеся в акрофазу хроноритма. После окончания курса терапии всем больным была произведена трансуретральная резекция простаты, после которой было проведено морфологическое и морфометрическое (иммуногистохимическое) исследование полученного материала.

Результаты. Согласно результатам морфологического и морфометрического исследования гистологического материала у пациентов ГС и ОГ были выявлены статистически значимые различия по всем исследуемым показателям, свидетельствующие о сохранении признаков воспалительного процесса в ГС, тогда как в ОГ выраженность воспаления была значительно ниже.

Заключение. Согласно результатам проведенного исследования, персонализированная комплексная терапия пациентов с доброкачественной гиперплазией предстательной железы в сочетании с хроническим простатитом с использованием комбинированного физиотерапевтического воздействия аппаратом «Смарт-Прост» с учетом индивидуальных хронобиологических особенностей пациентов позволяет более эффективно купировать воспалительный процесс в ткани предстательной железы, что может приводить к снижению количества послеоперационных осложнений. Однако последнее утверждение требует дальнейшего более детального изучения.

Ключевые слова: хронический бактериальный простатит; доброкачественная гиперплазия предстательной железы; ДГПЖ; ТУР простаты; хронотерапия; физиотерапия аппаратом «Смарт-Прост»; морфометрия; иммуногистохимия.

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common diseases in older men. The histological signs of BPH are found in 40% of men aged 50–59 years and in >75% of men aged ≥60 years, and clinical manifestations of the disease are detected in 20% and >35%, respectively [1–3]. According to some reports, chronic prostatitis (CP) is the most common urological disease in men aged <50 years and the third most frequent disease in men aged >50 years [4–7]. Accordingly, it is quite appropriate to assume that a combination of BPH and CP is highly probable in older men. The results of the morphological examination of the prostate tissue in these patients most accurately confirm the presence of BPH and CP.

According to the National Institutes of Health, >25% of men with urinary system diseases have symptoms of prostatitis, which constitute approximately 9% of the entire male population [5]. Results of morphological studies conducted in male patients with BPH indicate that signs of chronic inflammation of varying severities in the prostate tissue were present in 96.7% of the cases [8–12].

Histologically, CP in the active phase is manifested by the presence of alterative–exudative changes in the glandular and stromal tissues of the prostate, an increase in the number of segmented leukocytes, formation of pseudo-abscesses in the lumens of the glands, and emergence of the foci of new connective (granulation) tissues [13]. The inflammatory process in the prostate gland deteriorates significantly the clinical manifestations of BPH and increases the probability of postoperative complications. Inflammation is also significant in the mechanism of prostate enlargement due to cytokines secreted by macrophages [14].

Currently, transurethral resection (TUR) of the prostate is considered the gold standard of surgical treatment of patients with BPH [1, 15]. The indication for surgery is the presence of infravesical obstruction [16]. However, despite its advantages, TUR is accompanied by a rather high frequency of complications, including the most fatal ones for the patient's health, including hemorrhage (2.9%), urinary bladder tamponade (4.9%), infectious and inflammatory diseases (4.1%), urethral stricture (5%–7%), and urinary bladder neck sclerosis (2%–4%) [17, 18].

Given the insufficient efficiency of the known treatment methods for CP and BPH, alternative therapeutic methods with a proven pathophysiological mechanism of action become increasingly common in medicine, particularly in urology [19–22]. Various physiotherapeutic procedures have been recently used in combination with other drugs, such as magnetotherapy, electrophoresis, and laser therapy [23].

All processes in the wildlife, and hence in the human body, are subject to certain rhythms [19]. In the different phases of the rhythm, the physiological activities in the body are at different levels. Personalization of the treatment of patients, taking into account the individual characteristics of their biorhythms (chronotherapy) is a topic in many branches of medicine, including urology, and is widely used in the treatment of several diseases [20]. Chronotherapy consists of the graphic determination of the time when the chronobiological activity of each patient is at its maximum value (acrophase) and in performing medical procedures at this particular time [19–21].

This study aimed to assess the efficiency of personalized complex treatment of patients with prostate adenoma and CP using the Smart-Prost device in the acrophase of the chronorhythm based on the results of the morphological and morphometric examinations of histological materials obtained during TUR of the prostate.

MATERIALS AND METHODS

We examined 60 patients with BPH who were referred for surgical treatment (TUR of the prostate) and who were diagnosed with category II CP according to the classification of the USA National Institute of Health (NIH, 1995). The average age of the patients was 60.5 ± 5.5 years. The average duration of chronic bacterial prostatitis and BPH at the time of patient inclusion in the study was 7.5 ± 2.3 years.

The inclusion criteria were total IPSS score >20, residual urine volume not more than 100 ml, maximum urine flow rate of ≤14 ml/s, prostate gland volume of not more than 80 cm^3, prostate-specific antigen level in the blood serum of not more than 2.0 ng/ml, absence of sexually transmitted infections, bacterial nature of inflammation in the prostate gland (microbial count $>10^4$ CFU/ml in the prostate secretion), and duration of CP and BPH from 5 to 10 years.

The exclusion criteria were stones in the bladder and ureters, hematuria, suspected prostate or bladder cancer, allergic reactions to the drugs used, a history of surgical aids on the pelvic organs, urinary tract infections, neurogenic bladder dysfunction, abnormal development of the urinary and genital organs, oncological and severe cardiovascular diseases, diabetes mellitus, and hypogonadism.

The patients were randomly distributed into two groups of 30 people each. The comparison group (CG) included

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patients who received standard therapy with alpha-blockers (tamsulosin 0.4 mg once a day) and fluoroquinolones (levofloxacin 500 mg once a day), with a treatment course of 28 days. If necessary, the therapy was adjusted based on the sensitivity of microorganisms.

The main group (MG) consisted of patients who received standard therapy in combination with physiotherapy sessions with the Smart-Prost apparatus, which were performed in the chronorhythm acrophase. The chronorhythm was recorded every day at 8:00 using the Dinamika computer complex, after which the time corresponding to the maximum peak of the chronobiological activity of the patient's body (chronorhythm acrophase) was determined.

After the therapy, all patients underwent TUR of the prostate, and a morphological and morphometric (immunohistochemical) study of the material obtained was performed.

For histological examination, the prostate tissue was fixed in a 10% solution of neutral formalin. The tissue was dehydrated in ethyl alcohol of increasing concentration, and the biopsy sample was then embedded in paraffin. Sections of prostate tissue with a thickness of 5 μm were stained with hematoxylin and eosin, as well as picro-fuchsin according to Van Gieson, to identify collagen fibers. To detect plasma cells in paraffin sections, the immunohistochemical method was used. Monoclonal murine antibodies to human CD138 and clone M115 from DakoDenmark A/C (Denmark) were used. For this purpose, the immunoreactivity of primary antibodies was detected using secondary antibodies conjugated to the peroxidase system. Cell antigens were detected by an indirect enzyme-linked immunosorbent assay using the "EnVision FLEX+, PH, Mouse, high Ph" detection system made by DacoDenmark A/S. For the laboratory studies, an open-type auto-steiner Dako Link with a manual setting from the same manufacturer was used.

Biopsy samples (surgical material) were examined under a LeicaDMR light microscope using the LASVersion 4.4.0 software made by Leica Microsystems CMS GmbH (Switzerland). Tissue photomicrographs were taken in random areas of prostate fragments in each group. In total, 347 microphotographs were assessed in the CG, and 603 micrographs were analyzed in the MG (Fig. 1, 2).

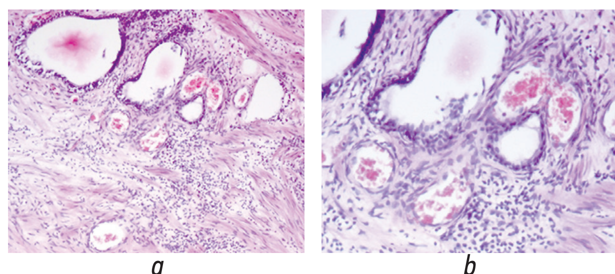
To measure the area of collagen fibers, the ImageJ 1.51t software (National Institutes of Health, USA) was also used. Histological sections of prostate tissue stained with picro-fuchsin according to Van Gieson were photographed using a computer image analysis system based on a LeicaDMR microscope, a Leica DFC295 digital camera, and a Leica digitization board (Germany) (Fig. 3).

When quantifying red-colored collagen, the RGB image was divided into red, green, and blue channels since the threshold tool functions only with grayscale images (Fig. 4). Then, using the threshold tool, the collagen was isolated in the most contrasting green channel, and a morphometric study was performed (Fig. 5).

The results of measuring the area of collagen in micrometers and the percentage of the area of the collagen from the entire area of each microphotograph were entered into a table by the program for subsequent statistical processing. In addition to the percentage of fibrosis area, the maximum threshold value of the pixels included in the measurements was calculated. This characteristic may indicate the intensity of the color of the collagen fibers.

The diameters of the arterioles and venules were also measured without dividing them into groups. According to Ham-Cormack, the average size of the lumen area of the arteriole is 452.16 μm^2 and that of the venule is 684.12 μm^2. Vascular diameters were measured using the LASVersion 4.4.0 software on microphotographs of the prostate gland sections stained with hematoxylin and eosin at a magnification of ×200 (Fig. 6).

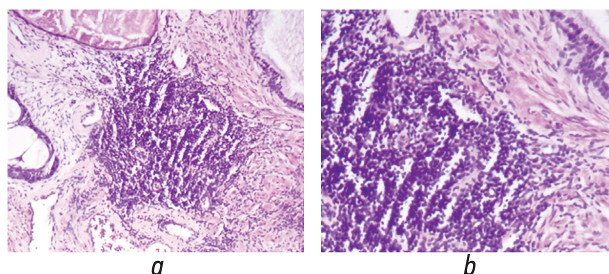
Statistical analysis was performed using the Statistica 10.0 (StatSoft) package. The conformity of the distribution



a *b*

Fig. 1. Micrograph of the preparation. Chronic prostatitis, inflammatory infiltrate in the stroma, hematoxylin-eosin staining, ×100 (*a*) and ×200 (*b*)

Рис. 1. Микрофотография препарата. Хронический простатит, воспалительный инфильтрат в строме, окраска гематоксилином и эозином, увеличение ×100 (*a*) и ×200 (*b*)



a *b*

Fig. 2. Micrograph of the preparation. Chronic prostatitis, the formation of a lymphoid follicle, hematoxylin-eosin staining, ×100 (*a*) and ×200 (*b*)

Рис. 2. Микрофотография препарата. Хронический простатит, формирование лимфоидного фолликула, окраска гематоксилином и эозином, увеличение ×100 (*a*) и ×200 (*b*)

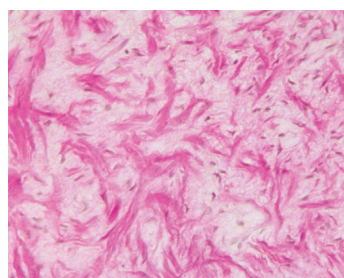


Fig. 3. Micrograph of the preparation. Van Gieson's picrofuchsin staining of collagen fibers, ×20
Рис. 3. Микрофотография препарата. Окраска коллагеновых волокон пикрофуксином по Ван Гизону. Увеличение ×20

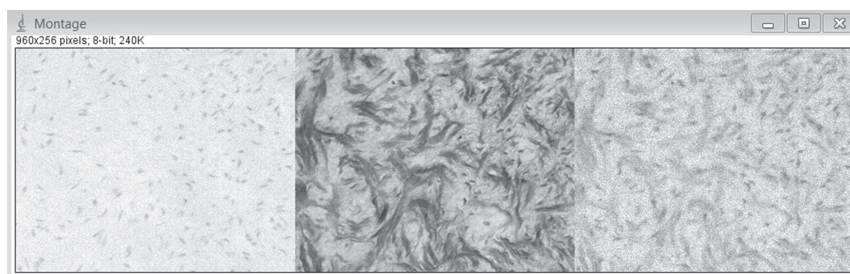


Fig. 4. Micrograph of the area of fibrosis. Split into three channels: red, green, blue
Рис. 4. Микрофотография области фиброза. Разделение на три канала: красный, зеленый, синий

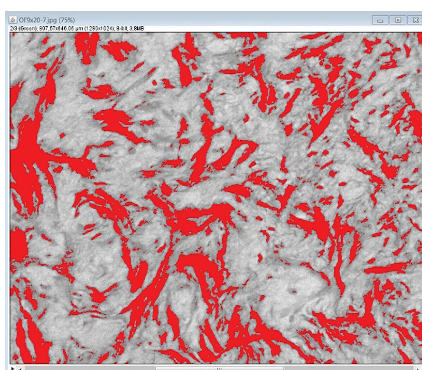


Fig. 5. Micrograph of a sample. Collagen fibers isolated with the "Threshold" tool
Рис. 5. Микрофотография образца. Коллагеновые волокна, выделенные с помощью инструмента «Threshold»

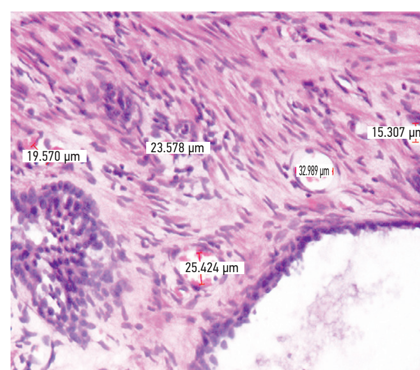


Fig. 6. Micrograph of a sample. Prostate. Measurement of vessel diameters. Hematoxylin-eosin staining, ×200
Рис. 6. Микрофотография образца. Простата. Измерение диаметров сосудов. Окраска гематоксилином и эозином, ×200

of quantitative data to a normal distribution was tested using the Shapiro–Wilk *W*-test. Two samples of quantitative characteristics were compared using the *t*-test for independent variables, since the variables had a normal distribution. The result was significant if the probability of rejecting the null hypothesis of the absence of differences did not exceed 5% ($p < 0.05$).

RESULTS

Fibrosis in the prostate gland is caused by the influence of various damaging factors on the parenchyma, including a chronic inflammatory process, and it is also a result of metabolic disorders in the prostate accompanied by BPH. Morphological examination reveals signs of structural changes, which are expressed by the accumulation of the extracellular matrix (ECM). ECM molecules combined to form large molecules of collagen, elastin, and other structures. Collagen is known to be the main structure that forms the gland stroma, and excessive formation of these structures leads to an impairment of the organ's function.

Table 1 presents the relative proportions of fibrous tissues in the prostate gland of patients of the MG and CG.

Table 1. The proportion of fibrosis in the prostate gland of patients in the comparison group and the main group ($n = 60$)
Таблица 1. Доля фиброза в предстательной железе пациентов группы сравнения и основной группы ($n = 60$)

Group (number of patients, *n*)	Number of samples	Average value, %	Minimum, %	Maximum, %	σ	*m*
Comparison group ($n = 30$)	347	35.47	10.96	57.18	9.04	0.49
Main group ($n = 30$)	603	19.89*	3.94	56.74	6.54	0.27

* The difference with the value in the comparison group is significant ($p < 0.05$).

Table 2. Comparative analysis of the number of plasma cells in the prostate gland of patients in the comparison group and the main group (*n* = 60)

Таблица 2. Сравнительный анализ количества плазматических клеток в предстательной железе пациентов группы сравнения и основной группы (*n* = 60)

Group (number of patients, *n*)	Number of fields of view	Number of cells positive for CD138 in 20 fields of view, ×20	Average number of plasma cells in the field of view
Comparison group (*n* = 30)	200	1178	5.89
Main group (*n* = 30)	200	290*	1.45*

* The difference with the value in the comparison group is significant ($p < 0{,}05$).

Table 3. Comparative analysis of measuring the diameter and area of the vessels of the microvasculature of the prostate gland in patients of the comparison group and the main group (*n* = 60)

Таблица 3. Сравнительный анализ измерения диаметра и площади сосудов микроциркуляторного русла предстательной железы пациентов группы сравнения и основной группы (*n* = 60)

Group (number of patients, *n*)	Number of fields of view	Number of measurements	Average vessel diameter, μm	Average area of the vessel lumen, $μm^2$
Comparison group (*n* = 30)	206	854	53.098	2834.393
Main group (*n* = 30)	301	1089	27.253*	794.539*

* The difference with the value in the comparison group is significant ($p < 0.05$).

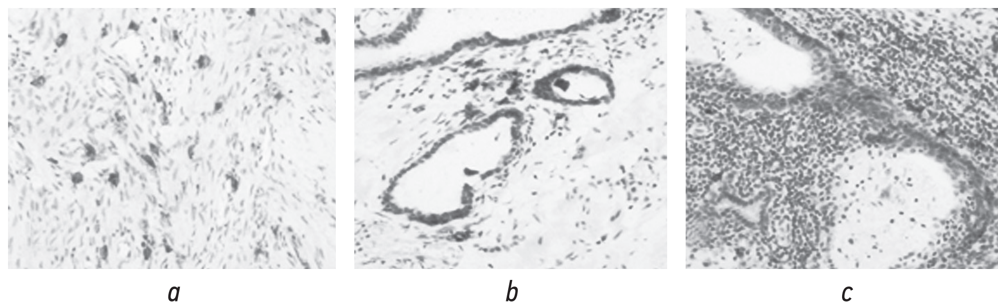


Fig. 7. Immunohistochemical study of plasma cells, reaction with CD138, ×200: *a* – plasma cells in the stroma; *b* – plasma cells in the stroma between the glands of the prostate; *c* – plasma cells in the lymphoid follicle

Рис. 7. Иммуногистохимическое исследование плазматических клеток, реакция с CD138, увеличение ×200: *a* — плазматические клетки в строме; *b* — плазматические клетки в строме между простатическими железами; *c* — плазматические клетки в лимфоидном фолликуле

The proportion of fibrous tissue in the MG was significantly less than that in the CG. Table 2 shows the results of a comparative analysis of the number of plasma cells in the CG and MG. Plasmocytes were indicated by immunohistochemical method using antibodies to CD138 (Fig. 7).

The number of plasma cells in the prostate gland, determined by immunohistochemical analysis, was significantly lower in the MG than in the CG. A similar tendency was noted when evaluating the results of measuring the diameter and area of the vessels of the prostatic microvasculature (Table 3).

According to the results of the morphological and morphometric study of the histological materials of the prostate gland of patients in the CG and MG, significant differences were found in all parameters examined, indicating the persistence of inflammatory signs in the CG, while its severity in the MG was significantly lower.

DISCUSSION

In chronic inflammation, active inflammation, tissue damage, and repair occur simultaneously. In the histological material obtained after TUR of the prostate, the five main morphological signs of chronic inflammation include the presence of a productive tissue reaction with infiltration by mononuclear cells (macrophages, lymphocytes, and plasma cells), as well as repair failure, angiogenesis, and tissue sclerosis [13]. Although the main cells of chronic inflammation are macrophages, we selected the count of plasma cells in biopsy samples of the prostate gland for this study. Plasma cells, as immunocompetent cells of the lymphocytic series, producing antibodies, are directed

against a persistent antigen in the focus of inflammation or against components of destroyed tissue. They represent a common morphological indicator of chronic inflammation and its intensity.

In the MG, significant differences ($p < 0.05$) were found in all morphometric and immunohistochemical parameters examined when compared with the CG. The proportion of fibrous tissue in the prostate of the MG was significantly less than that in the CG. In addition, the MG had a lower intensity of fibrosis development, as evidenced by the higher optical density of collagen in the patients, which indicated its maturity. A similar presentation is typical for the end of the fibrosis process. In addition, significant differences were registered in the area of blood vessels and number of plasma cells. All these changes indicate a more effective and quicker relief of the inflammatory process in the prostate tissue in patients who received standard therapy in combination with physiotherapy sessions using the Smart-Prost apparatus in the chronorhythm acrophase for 4 weeks.

Despite the relatively small amount of data on the changes of the morphological and morphometric parameters with time in the prostate tissue under various physical effects, the results in this study are consistent with those of other studies [13], which also demonstrated the efficiency of personalized complex treatment of patients with BPH and CP.

CONCLUSION

According to the results of this study, personalized comprehensive therapy of patients with BPH and CP using a combined physiotherapeutic effect of the Smart-Prost apparatus, taking into account the individual chronobiological characteristics of the patients, ceases more effectively the inflammatory process in the prostate tissue. This mechanism can decrease the number of postoperative complications; however, more detailed studies are needed.

REFERENCES

1. Alyaev YuG, Glybochko PV, Pushkar' DYu [editors]. *Urologiya. Rossiiskie klinicheskie rekomendatsii*. Moscow: GEOTAR-Media, 2018. 480 p. (In Russ.)

2. Gravas S, Cornu JN, Gacci M, et al. Management of non-neurogenic male lower urinary tract symptoms (LUTS) [Internet]. *EAU-Guideline*. 2020 [cited 01.06.2021]. Available from: https://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts.

3. Roehrborn CG. *Benign Prostatic Hyperplasia: Etiology, Pathophysiology, Epidemiology, and Natural History*. Campbell-Walsh. Urology, 10th edition. 2012. P. 2570–2610. DOI: 10.1016/B978-1-4160-6911-9.00091-8

4. Kuz'menko AV, Kuz'menko VV, Gyaurgiev TA. Combination drug therapy in patients with BPH. *Urologiia.* 2018;(1):101–105. (In Russ.) DOI: 10.18565/urology.2018.1.101-105

5. Schaeffer AJ. Classification (Traditional and National Institutes of Health) and Demographics of Prostatitis. *Urology*. 2002;60(6):5–6. DOI: 10.1016/s0090-4295(02)02292-6

6. Nickel J. Prostatitis. CUA Guidelines. *Can Urol Assoc J*. 2011;5(5):306–315. DOI: 10.5489/cuaj.11211

7. Rees J, Abrahams M, Doble A, Cooper A. 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(4):509–525. DOI: 10.1111/bju.13101

8. Kudryavcev YuV, Sivkov AV. Morphological alteration in benign prostatic hyperplasia tissue. *Experimental & clinical urology*. 2010;(1):18–22. (In Russ.)

9. Bartoletti R, Cai T, Mondaini N, 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 multicenter case-control observational study. *J Urol*. 2007;178(6):2411–2415. DOI: 10.1016/j.juro.2007.08.046

10. Huang XH, Qin B, Liang YW. LUTS in BPH patients with histological prostatitis before and after transurethral resection of the prostate. *Zhonghua Nan KeXue*. 2013;19(1):35–39. (In Chinese).

11. 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). *Can Urol Assoc J*. 2014;8(11–12):403–408. DOI: 10.5489/cuaj.2179

12. Asgari SA, Mohammadi M. The role of intraprostatic inflammation in the acute urinary retention. *Int J Prev Med.* 2011;2(1):28–31.

13. Logvinov LA. *Kliniko-morfologicheskie kharakteristiki khronicheskogo prostatita* [dissertation]. Moscow, 2008. (In Russ.)

14. Vaupel P, Kelleher DK. Blood flow and oxygenation status of prostate cancers. *Adv Exp Med Biol*. 2013;765:299–305. DOI: 10.1007/978-1-4614-4989-8_42

15. Mustafaev AT, Kyzlasov PS, Dianov MP, et al. Surgical treatment of benign prostatic hyperplasia: the past and the present. *Urologicheskie vedomosti*. 2019;9(1):47–56. (In Russ.) DOI: 10.17816/uroved9147-56

16. Al'-Shukri SKh, Tkachuk VN, Gorbachev AG, et al. Urodinamicheskie issledovaniya v diagnostike infravezikal'noi obstruktsii u muzhchin. *Urologiya i nefrologiya*. 1998;(6):27–29. (In Russ.)

17. Kuz'menko AV, Kuz'menko VV, Gyaurgiev TA. The efficacy of fesoterodine in patients after transurethral resection of the prostate. *Urologiia.* 2019;(1):52–55. (In Russ.) DOI: 10.18565/urology.2019.1.52-55

18. Martov AG, Merinov DS, Kornienko SI, et al. Posleoperatsionnye urologicheskie oslozhneniya transuretral'nykh ehlektrokhirurgicheskikh vmeshatel'stv na predstatel'noi zheleze po povodu adenomy. *Urologiia*. 2006;(2):25–31. (In Russ.)

19. Kuzmenko AV, Kuzmenko VV, Gyaurgiev TA, Barannikov II. Chronobiological status of patients with chronic prostatitis and prostate adenoma. *System analysis and management in biomedical systems*. 2017;16(3):513–516. (In Russ.)

20. Lanina VA, Khimicheva MN, Kuz'menko VV, et al. Khronobiologicheskie osobennosti bol'nykh s khronicheskim prostatitom pri adenome prostaty. *Tendentsii razvitiya nauki i obrazovaniya*. 2020;(66–1):111–114. (In Russ.)

21. Barannikov II, Kuzmenko AV, Gyaurgiev TA, Kuzmenko VV. Evaluation of the effectiveness of personalized complex therapy in patients with benign prostatic hyperplasia and chronic prostatitis. *Urology reports (St. Petersburg)*. 2021;11(1):39–48. (In Russ.) DOI: 10.17816/uroved56773

22. Al-Shukri SKh, Gorbachev AG, Borovets SYu, et al. Prostatilen treatment of prostatic adenoma. *Urologiia*. 2006;(6):22–25. (In Russ.)

23. Bokov AI, Zabelin MV, Kyzlasov PS. Efficiency of physiotherapy treatment of chronic bacterial prostatitis. *Urologicheskie vedomosti*. 2016;6(1):10–15. (In Russ.) DOI: 10.17816/uroved6110-15

СПИСОК ЛИТЕРАТУРЫ

1. Урология. Российские клинические рекомендации. Под ред. Ю.Г. Аляева, П.В. Глыбочко, Д.Ю. Пушкаря. М.: ГЭОТАР-Медиа; 2018. 480 с.

2. Gravas S., Cornu J.N., Gacci M., et al. Management of non-neurogenic male lower urinary tract symptoms (LUTS) [Internet]. EAUGuideline. 2020. Дата обращения: 01.06.2021. Доступ по ссылке: https://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts.

3. Roehrborn C.G. Benign Prostatic Hyperplasia: Etiology, Pathophysiology, Epidemiology, and Natural History. Campbell-Walsh. Urology, 10th edition. 2012. P. 2570–2610. DOI: 10.1016/B978-1-4160-6911-9.00091-8

4. Кузьменко А.В., Кузьменко В.В., Гяургиев Т.А. Комбинированная медикаментозная терапия пациентов с аденомой предстательной железы // Урология. 2018. № 1. С. 101–105. DOI: 10.18565/urology.2018.1.101-105

5. Schaeffer A.J. Classification (Traditional and National Institutes of Health) and Demographics of Prostatitis // Urology. 2002. Vol. 60. No. 6. P. 5–6. DOI: 10.1016/s0090-4295(02)02292-6

6. Nickel J. Prostatitis. CUA Guidelines // Can Urol Assoc J. 2011. Vol. 5. No. 5. P. 306–315. DOI: 10.5489/cuaj.11211

7. Rees J., Abrahams M., Doble A., Cooper A. 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. Vol. 116. No. 4. P. 509–525. DOI: 10.1111/bju.13101

8. Кудрявцев Ю.В., Сивков А.В. Морфологические изменения ткани предстательной железы при доброкачественной гиперплазии // Экспериментальная и клиническая урология. 2010. № 1. С. 18–22.

9. Bartoletti R., Cai T., Mondaini N., 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 multicenter case-control observational study // J Urol. 2007. Vol. 178. No. 6. P. 2411–2415. DOI: 10.1016/j.juro.2007.08.046

10. Huang X.H., Qin B., Liang Y.W. LUTS in BPH patients with histological prostatitis before and after transurethral resection of the prostate // Zhonghua Nan KeXue. 2013. Vol. 19. No. 1. P. 35–39.

11. 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) // Can Urol Assoc J. 2014. Vol. 8. No. 11–12. P. 403–408. DOI: 10.5489/cuaj.2179

12. Asgari S.A., Mohammadi M. The role of intraprostatic inflammation in the acute urinary retention // Int J Prev Med. 2011. Vol. 2. No. 1. P. 28–31.

13. Логвинов Л.А. Клинико-морфологические характеристики хронического простатита: дис. … канд. мед. наук. Москва, 2008.

14. Vaupel P., Kelleher D.K. Blood flow and oxygenation status of prostate cancers // Adv Exp Med Biol. 2013. Vol. 765. P. 299–305. DOI: 10.1007/978-1-4614-4989-8_42

15. Мустафаев А.Т., Кызласов П.С., Дианов М.П., и др. Хирургическое лечение доброкачественной гиперплазии предстательной железы: прошлое и настоящее // Урологические ведомости. 2019. Т. 9, № 1. С. 47–56. DOI: 10.17816/uroved9147-56

16. Аль-Шукри С.Х., Ткачук В.Н., Горбачев А.Г., и др. Уродинамические исследования в диагностике инфравезикальной обструкции у мужчин // Урология и нефрология. 1998. № 6. С. 27–29.

17. Кузьменко А.В., Кузьменко В.В., Гяургиев Т.А. Эффективность применения фезотеродина у больных после трансуретральной резекции предстательной железы // Урология. 2019. № 1. С. 52–55. DOI: 10.18565/urology.2019.1.52-55

18. Мартов А.Г., Меринов Д.С., Корниенко С.И., и др. Послеоперационные урологические осложнения трансуретральных электрохирургических вмешательств на предстательной железе по поводу аденомы // Урология. 2006. № 2. С. 25–31.

19. Кузьменко А.В., Кузьменко В.В., Гяургиев Т.А., Баранников И.И. Хронобиологический статус больных хроническим простатитом на фоне аденомы предстательной железы // Системный анализ и управление в биомедицинских системах. 2017. Т. 16. № 3. С. 513–516.

20. Ланина В.А., Химичева М.Н., Кузьменко В.В., и др. Хронобиологические особенности больных с хроническим простатитом при аденоме простаты // Тенденции развития науки и образования. 2020. № 66–1. С. 111–114.

21. Баранников И.И., Кузьменко А.В., Гяургиев Т.А., Кузьменко В.В. Оценка эффективности персонализированной комплексной терапии пациентов с доброкачественной гиперплазией простаты и хроническим простатитом // Урологические ведомости. 2021. Т. 11, № 1. С. 39–48. DOI: 10.17816/uroved56773

22. Аль-Шукри С.Х., Горбачев А.Г., Боровец С.Ю., и др. Лечение больных аденомой предстательной железы простатиленом // Урология. 2006. № 6. С. 22–25.

23. Боков А.И., Забелин М.В., Кызласов П.С. Эффективность физиотерапевтического лечения хронического бактериального простатита // Урологические ведомости. 2016. Т. 6, № 1. С. 10–15. DOI: 10.17816/uroved6110-15

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