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ФГАОУ ВО ПЕРВЫЙ МОСКОВСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ ИМЕНИ И.М. СЕЧЕНОВА МИНИСТЕРСТВА ЗДРАВООХРАНЕНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ (СЕЧЕНОВСКИЙ УНИВЕРСИТЕТ)

UROLOGIIA

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ООО «БИОНИКА МЕДИА ИННОВАЦИИ»

CONTENTS

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TO THE 100TH ANNIVERSARY OF THE JOURNAL "UROLOGIIA"

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In March 2023, the journal Urologiia turned 100 years old. In the 2nd issue, which is the jubilee for the journal, we traditionally provide a summary of the results of last five years of work.

The journal highlights the latest achievements in the field of urology, andrology, nephrology and oncourology. The advanced experience in studying the etiology, pathogenesis, new methods of diagnostics, prevention and treatment of kidney diseases is presented. Among other important topics are the pathological conditions of genitourinary system, inflammatory processes of various etiologies, urolithiasis, renal failure, reconstructive procedures, andrology and pediatric urology. The journal «Urologiia» publishes original and discussion articles, lectures, literature reviews, clinical observations and new medical technologies. The readership of the journal is urologists, andrologists, nephrologists, surgeons, obstetricians-gynecologists, pediatricians and general practitioners. The role of the journal «Urologiia» as a source of fundamental and clinical knowledge and its contribution to the education of many generations of Russian scientific and medical personnel is invaluable. For all doctoral and the vast majority of candidate dissertations, a criterion of their scientific and practical significance is the publication in journal «Urologiia».

A new stage of the development of the journal started within a comprehensive program of innovative reforms of the Russian Society of Urology. Since May 2012, the journal has been published by Bionika Media LLC. The publishing house presents many specialized projects in the field of medicine and pharmacy. With the transition to a new publishing house, the journal has had its own Web site (www.urologyjournal.ru), which meets all the criteria of modern scientific publications. All users are given access to the archive of issues. In addition, there is information on the rules and procedures for filing applications for publications and a possibility of subscribing to sending articles to the editor online.

The journal is cited in the international database PubMed, Medline, Scopus, EBSCO, and is included in the List of journals recommended by the Higher Attestation Commission for publishing research results of candidate and doctoral dissertations. It is distributed at all specialized exhibitions, congresses and conferences [1].

The working group of the Higher Attestation Commission under the Ministry of Education and Science of Russia, together with the expert councils of the Higher Attestation Commission, based on the analysis of scientometric indicators (a coefficient of scientific significance), the journal «Urologiia» was included in the List of journals of the K1 category.

Since 2013, the editor-in-chief of the journal «Urologiia» is a corresponding member of RAS, Honorary Head of the Department of Urology, FGAOU VO "First Moscow State Medical University named after I.M. Sechenov" of the Ministry of Health of Russia, Professor Yu.G. Alyaev. The permanent deputy editor-in-chief of the journal is the head of the department of urology and andrology, MBU INO FMBC named after A.I. A.I. Burnazyan FMBA of Russia, corresponding member of RAS, professor A.G. Martov. The executive secretary of the journal is the head of the department of urology of the Department of Urology, GBUZ MO MONIKI. M.F. Vladimirsky, prof. V.V. Dutov. Since 2014, the scientific editor of the journal is MD. Z.K. Gadzhieva. The head of the editorial board is E.V. Polyakova.

Over the past 5 years, the editorial board of the journal has been expanded. It is now included professors Kh.S. Ibishev, A.Yu. Pavlov, S.V. Kotov, A.A. Kostin, N.K. Gadzhiev, T.S. Perepanova, G.V. Kozyrev. The editorial board of the journal «Urologiia» also consists of foreign professors, like K.G. Naber (Professor, Clinical Hospital at the Technical University of Munich, Germany), Ch.R. Chapple (Professor, Secretary General of the European Association of Urology), M. P. Wirth (Professor, representative of the European Association of Urology), B.U. Shalekenov (MD, Prof., Head of the Department of Urology and Andrology, Kazakh Medical University of Continuing Education, Almaty [Kazakhstan]), A.V. Strotsky (D.M.S., Prof., Belarusian State Medical University, Minsk [Belarus]), A.A. Muradyan (D.M.S., Prof., Head of the Department of Urology, Yerevan State Medical University after Mkhitar Heratsi, Yerevan [Armenia]).

Since 2015, the English version of the journal continues to be published, in which the best articles published in the Urology journal are presented. The leader and ideological inspirer of this project is the Executive Director of the Regional Educational Institution, Director of the National Medical Research Center for the profile «Urologiia» of the FGAOU VO "First Moscow State Medical University named after I.M. Sechenov" of the Ministry of Health of Russia, professor M.A. Gazimiev. The English version is posted on the journal's website.

In collections for 2021–2022 a total of 40 articles have been published. Currently, work is underway on the next collection.

We are pleased to share good news about the growth of our publication's subscription over the past 5 years. Thanks to our loyal readers and partners, we were able to increase the number of journal subscribers by several times, which indicates the high appreciation of our work and the importance of the scientific materials that we provide.

The journal «Urologiia» is distributed not only in Russia, but also abroad. Libraries of many CIS members, China and neighboring countries also subscribe to our journal, which confirms its authority and relevance in the world scientific community.

The leaders in subscription to the journal «Urologiia» are the Russian regions, such as Moscow, St. Petersburg, Krasnoyarsk, Novosibirsk, Kazan. We thank all our readers for their trust and interest in our journal and promise to continue to delight you with new scientific discoveries and researches in the field of urology.

Both paper and electronic versions of our publication are available in the publishing house. If you are already subscribed or plan to subscribe to the paper version, then you can also access the electronic version. To do this, you must register when subscribing to the publisher. If you are already registered, then after paying for the subscription, access to the electronic version will be provided automatically. We are always ready to provide our readers with maximum comfort when reading the magazine.

Over the past 5 years, the volume of published issues of the journal and, accordingly, the number of articles in each issue has increased significantly. A volume of issue has changed from 120 to 180 pages. A total of 777 scientific articles were published (excluding anniversaries, obituaries, resolutions), of which 510 were cited.

Since 2018, 6 issues of the journal have been published every year. However, in 2018 a total of 173 articles (1004 pages) and 1 supplement (4 articles, 52 pages) were prepared, compared to 160 articles (960 pages) in 2019, 146 articles (900 pages) in 2020, 145 articles (912 pages) in 2021 and 153 articles (872 pages) in 2022.

Such an active work is the result of the editorial board and the editorial board of the journal following the main goals and objectives that were previously defined for the journal [1].

Goals and objectives of the journal «Urologiia»:

- publish high-quality scientific articles that meet international standards for scientific work;
- increase the level of reviewing and editing of articles submitted for publication;
- ensure the widest possible dissemination of published articles in the world scientific community;
- to expand the possibilities of dissemination and indexing of scientific works in various key foreign citation bases.

The work of the journal continues. More and more attention is paid to interdisciplinary issues of diagnosis and treatment of urological diseases. Authors from Moscow, St. Petersburg, Rostov-on-Don, Novosibirsk and Voronezh are leading in terms of publications in the journal. The articles written by colleagues from the CIS and abroad are regularly published. Works sent by foreign colleagues are published in English.

The 2-year impact factor of the journal "Urologiia" according to the RSCI is 0.734, while 5-year is 0.642. 10-year Hirsch index is 21 (see table) [2].

The journal continues to develop and be indexed in international databases. Over the past 5 years, the journal «Urologiia» has been moved in the Scopus database from the fourth quartile (Q4) to the third (Q3). This is a very important achievement of the authors and editors of the journal. The number of citations of articles in Scopus has increased by about 3 times, which underlines the quality of published materials that meet international standards. CiteScore have risen from 0.2 in 2018 to 0.6 in 2021.

Continuing the traditions of the journal in the year of its 100th anniversary, we would like to repeat that it is in our plans and intentions to continue to make every effort to continuously improve the quality of the form and content

Table

The indicators of improvement of the journal "Urologiia" according to the statistics of the RSCI (the date of updating the is March 7, 2023, data for 2022 will be formed in the RSCI in 2023) [2]

	2013	2014	2015	2016	2017	2018	2019	2020	2021
2-year impact factor of the RSCI	0.579	0.544	0.618	0.660	0.541	0.674	0.716	0.865	0.734
2-year impact factor adjusted for citations from all sources	0.746	0.789	0.761	0.748	0.730	0.835	0.895	0.946	0.882
Number of citations of articles of the previous 2 years	179	206	197	196	224	264	290	315	269
Quoting from the journals:	139	142	160	173	166	213	232	288	224
Quoting from the RSCI:	71	79	93	110	114	125	148	168	166
5-year impact factor of the RSCI	0,655	0,483	0,554	0,605	0,581	0,619	0,609	0,673	0,642
Number of citations of articles of the previous 5 years, including:	379	294	336	388	400	444	457	532	510
- citations from the RSCI	180	167	196	224	245	267	260	314	377
Average number of authors	279	290	365	362	393	397	436	458	426
Average H-index of authors	6,2	6,6	6,7	7,7	8,3	8,0	8,4	8,5	8,6
Decadal H-index	18	18	18	19	19	20	20	20	21
Number of article views per year	5817	4217	5884	16386	27013	17509	15790	19369	23182
Number of article downloads per year	6	18	40	680	517	726	713	697	1761

of the material provided to readers. The high status and authority that the publication has today is the result of hard, prolonged, painstaking, but at the same time fruitful work of the authors, the professional editorial board, the editorial staff and the publishing house. We wish the journal to always remain the "bible" of domestic urology and open up new horizons in its development, we promise to do everything that depends on us for this.

Journal «Urologiia» today is not just a publication, it is our mission and responsibility to readers. We are proud that we were able to achieve such high results in our work and we promise to continue to move only forward, opening up new horizons in science and medicine.

Thank you for being with us!

We are waiting for your articles on the pages of the journal «Urologiia».

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ASSESSMENT OF SEXUAL FUNCTION AND QUALITY OF LIFE IN WOMEN WITH POSTCOITAL CYSTITIS

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Introduction. According to the literature, 20-50% of women will experience urinary tract infection (UTI) in their lifetime, and in 10-30% of cases, cystitis will recur. Despite the high prevalence of recurrent UTI, there are lack of studies dedicated to its impact on the quality of life, and the influence of postcoital cystitis on the quality of life and sexual function has not been previously evaluated.
Aim. To assess the quality of life and sexual function in patients with recurrent postcoital cystitis before and after transposition of the urethra.
Material and methods. Women suffering from recurrent postcoital cystitis, who underwent urethral transposition from 2019 to 2021 were included the study. The SF-12v2 questionnaire was used to assess quality of life, while sexual function was evaluated using Female Sexual Function Index [FSFI]. Questionnaires were filled out by 70 patients, before and after surgery.
Results. All domains of the quality of life were significantly different in the pre- and postoperative period. More pronounced changes were found in the mental health-related quality of life. In addition, there were significant differences in each domain of FSFI and the overall score postoperatively compared to baseline.
Conclusion. Our study reports a high prevalence of sexual dysfunction among women with recurrent postcoital cystitis as well as a reduced quality of life. This work shows the social significance of the problem, as well as the high rehabilitation potential of urethral transposition.

K e y w o r d s: postcoital cystitis; recurrent urinary tract infection; quality of life; sexual function.

The authors declare that they have no conflicts of interest. For citation: Komyakov B.K., Shevnin M.V., Ochelenko V.A., Tarasov V.A., Klitsenko O.A. Assessment of sexual function and quality of life in women with postcoital cystitis. Urologiia. 2023;2:20–25
Doi: https: //dx.doi.org/10.18565/urology.2023.2.20-25

Introduction. Urinary tract infection (UTI) is one of the most common bacterial infections in the world. Its occurrence among women is significantly higher, which is explained by the anatomical features and location of the female urethra, which allow uropathogens to more easily enter the bladder before they are eliminated during urination. In addition, the external urethral orifice in women is located near the vagina and rectum, which are colonized by a large number of different bacteria.

According to the literature, 20–50% of women will experience cystitis during their lifetime, and in 10–30% of cases recurrent form occurs [1–4]. If the UTI recurs 3 times or more per year or there are 2 episodes in the last 6 months, then cystitis is considered recurrent [3]. The highest incidence rates of recurrent UTIs are in the age groups of 18–34 and 55–64 years [5]. Among the risk factors contributing to the recurrent UTIs in young patients are sexual intercourse, spermicide use, recurrent UTIs from childhood, having a mother with a history of UTIs, and dysfunctional urination [6, 7].

A special form of recurrent cystitis is postcoital cystitis, when an episode of bladder infection develops after sexual intercourse. In most patients, the manifestation is associated with the onset of sexual activity. In the absence of the effect of non-antibacterial prophylaxis, an extravaginal transposition of the urethra can be effectively used to prevent the recurrent postcoital cystitis [8, 9].

Lower UTIs are not associated with life-threatening conditions, but can significantly affect the quality of life, limiting daily activity, social life and work [10]. Quality of life assessment is widely used to analyze the impact of various diseases on physical and mental health. For these purposes, a lot of questionnaires have been developed. One of the them that is now widely used is SF-12v2 (12-Item Short Form Survey version 2.0). It has a relatively short form to fill out with comparable accuracy with the standard SF-36 [11].

The impact of acute lower UTI on quality of life has been described, in addition to the fact that clinical cure is associated with better quality of life compared to treatment failure [12]. A multinational study from Europe, which assessed changes in quality of life in women with recurrent cystitis, also shows a significant decrease in both physical and mental health [13].

For patients suffering from postcoital cystitis, an influence of the disease on the sexual activity, especially in its aggressive course, when cystitis occurs after each sexual intercourse, deserves special attention, since it can lead to the development of sexual dysfunction. Female sexual dysfunction is defined as a disorder of sexual desire, arousal, orgasm, dyspareunia, which lead to significant distress and has a negative impact on a woman's health and significantly affects the quality of life [12]. The problem of sexual dysfunction in women with lower urinary tract symptoms due to urinary incontinence or pelvic organ prolapse is thoroughly described in the literature. The prevalence of sexual dysfunction can reach up to 50% [14, 15]. However, studies evaluating the prevalence of sexual dysfunction in those with recurrent UTIs are sporadic [4].

Due to the lack of domestic and foreign publications devoted to the impact of postcoital cystitis on the quality of life and sexual function in women, as well as influence of urethral transposition, we have carried out this study.

Materials and methods. The study included women with recurrent postcoital cystitis who underwent extravaginal urethral transposition from 2019 to 2021. The SF-12v2 questionnaire was used to assess the quality of life, and the Female Sexual Function Index (FSFI) was chosen for an evaluation of sexual function. Questionnaires were filled out by 70 patients before and after surgery in latent phase (Table 1). The mean age of the patients was 29.1±5.5 years. Transposition of the urethra was performed according to the method of B.K. Komyakov, developed in our clinic [8]. The study included women in whom this procedure was considered successful, namely in the absence of episodes of cystitis or no more than 2 recurrences during the year. Patients who had not been sexually active during the 4-week period prior to the survey were not included. Only data from fully completed questionnaires were analyzed.

The SF-12v2 questionnaire consists of eight domains. Four domains reflect the physical and four mental components of the quality of life. The physical component domains include Physical functioning (PF), Role-physical (RP), Bodily pain (BP) and General health (GH), while the mental component scales include Vitality (VT), Social functioning (SF), Role-emotional (RE) and Mental health (MH). After summation, two scores, the physical (PCS) and mental components (MCS) of the quality of life, are formed. To simplify the analysis and to achieve a high level of comparability, normalized indicators were calculated for all scores, as well as for the total PCS and MCS scores in accordance with the normative values for population [11]. Thus, scores greater than 50 represent above average health status, while higher scores correspond to a better quality of life.

FSFI questionnaire included an assessment of sexual function during the last month before surgery, as well as in the postoperative period from the onset of sexual activity. It includes 19 questions regarding sexual desire, arousal, vaginal lubrication, satisfaction, orgasm frequency and intensity, and discomfort or pain during intercourse. Total score was then calculated, with the maximum result of 36 and the minimum of 2 points. The values were summarized after the recalculation of individual value for each item. Higher scores indicate a higher level of sexual functioning on the respective item. FSFI was evaluated according to the cut-off value of 26.55 proposed by Wiegel et al. SD [16].

Statistical analysis was carried out using the Statistica 10 software. In the absence of a normal distribution, quantitative data were described using the median (Me), lower and upper quartiles (Q1–Q3). Quantitative variables were analyzed using the Wilcoxon test, and independent samples were analyzed using the Mann Whitney U test. Comparisons of the proportions were evaluated using the McNemar's test. For preoperative data, an analysis was performed using the Spearman's rank correlation coefficient. One-way analysis of variance (ANOVA) and the Kruskal-Wallis test were also used. When significant differences were found between the groups, a pairwise comparison was additionally performed using Tukey test. Differences were considered significant at the $p<0.05$.

Results. All domains of the quality of life differed significantly in the pre- and postoperative periods (*Table 2*). More pronounced changes were noted in MCS (total score: 35.26 [26.85–42.77]). Analyzing the results of the survey, a high PF score both before and after transposition of the urethra was found. However, there were low values of the PF before the procedure, which provided a significant difference between the groups ($p=0.002$).

Table 1

Characteristics of patients

	Ranks	*n* (%)
n		70
Age, years (M)		19-42 (29.1)
BMI, kg/m^2 (M±SD)		20.6±1.83
Duration of the disease (M±SD)		8.1±4.4
Charlson Comorbidity Index, points	0	68 (97.1)
	1	2 (2.9)
Number of sexual contacts per month	1) от 1 до 4	30 (42.9)
	2) от 5 до 11	24 (34.3)
	3) 12 и более	16 (22.8)
The frequency of recurrences of cystitis per year	1) от 3 до 4	13 (18.6)
	2) от 5 до 9	23 (32.8)
	3) 10 и более	34 (48.6)
The effect of conservative (non-antibacterial) methods of prevention	Positive	19 (27.1)
	Negative	51 (72.9)

Table 2

Quality of life before and after surgery (SF 12v2)

Domain, score	Stages of follow-up, n=70						*P*-value
	до операции			после операции			
	Me	Q1–Q3	min-max	Me	Q1–Q3	min-max	
Physical functioning (PF)	56.47	56.47-56.47	22.11-56.47	56.47	56.47-56.47	47.88-56.47	0.002*
Role-physical (RP)	52.57	42.21-57.18	24.93-57.18	57.18	52.57-57.18	47.96-57.18	<0.001*
Bodily pain (BP)	47.25	26.87-57.44	16.68-57.44	57.44	47.25-57.44	26.87-57.44	
General health (GH)	44.74	29.65-44.74	18.87-55.52	55.52	55.52-61.99	44.74-61.99	
Vitality (VT)	47.75	37.69-47.75	27.62-57.81	57.81	47.75-57.81	37.69-67.88	
Social functioning (SF)	36.37	33.85-46.47	16.18-56.57	46.47	43.95-56.57	26.27-56.57	
Role-emotional (RE)	39.3	22.53-44.9	11.35-56.08	50.49	44.9-56.08	44.9-56.08	
Mental health (MH)	40.16	27.97-46.25	15.77-58.45	52.35	46.25-52.35	34.06-64.54	
Physical Component Summary (PCS)	51.89	45.53-56.25	22.88-64.4	57.05	55.46-58.9	44.44-62.67	
Mental Component Summary (MCS), M±SD	34.79±10.25		12.83-55.36	47.4±5.67		34.53-63.38	

* Changes are significant (p<0.05).

An analysis of the quality of sexual life also showed a pronounced difference both between each domain of FSFI questionnaire and the total score before surgery: 22 [18.3–24.8] vs. 29.3 [27.9–31.8] postoperatively, p<0.001 (*Table 3*). The lowest FSFI score before surgery was observed for pain (3.2 [2.8-3.6]) and desire (3.3 [2.4-4.2]). Their scores increased after urethral transposition. According to the recommended cut-off value of 26.55 points, the prevalence of sexual dysfunction was 88.6% vs. 10% prior and after surgery, respectively (x2=42.3; p<0.001). We also analyzed the results of surgical treatment of 8 (11.4%) patients who did not have sexual dysfunction at baseline. The total FSFI score was 27.3±0.7. Despite the high initial total FSFI, after the surgical procedure there was a significant increase by 31.2±2.3 (p=0.017). The most significant changes in these patients were observed in terms of pain and arousal, while there were no differences in an orgasm domain (p=0.1). Among 7 (10%) patients in whom after urethral transposition, according to the cut-off point of 26.55 points, sexual

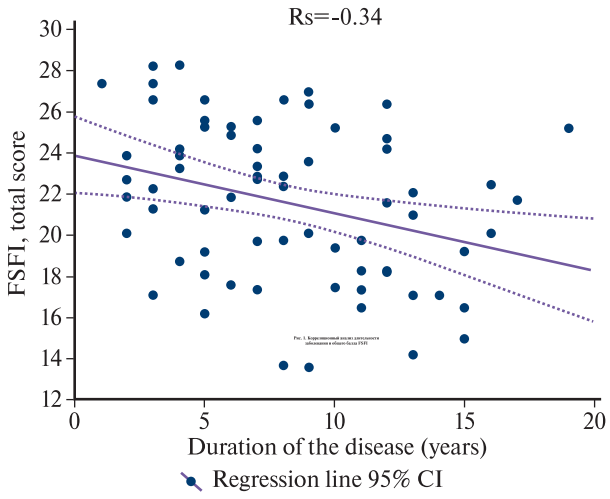

Fig. 1. Correlation analysis of duration of the disease and total FSFI score

Table 3

Quality of sexual life before and after surgery (FSFI)

Domain, score	Stages of follow-up, *n*=70						*P*-value
	At baseline			Postoperatively			
	Me	Q1-Q3	min-max	Me	Q1-Q3	min-max	
Desire	3.3	2.4-4.2	1.2-5.4	4.8	4.8-5.4	3.6-6	<0.001*
Arousal	3.6	3.3-4.5	1.5-5.1	5.4	4.8-5.7	3.6-6	
Lubrication	4.2	3.9-4.5	2.4-5.1	4.8	4.5-4.9	3.9-6	
Orgasm	3.6	2.8-4.8	1.2-5.6	4.8	4.4-5.6	1.6-6	
Satisfaction	3.6	2.8-4.4	1.6-5.2	5.2	4.8-5.7	4-6	
Pain	3.2	2.8-3.6	1.6-5.6	4.8	4.3-5.2	3.2-6	
Total score, M±SD	21.6 ± 3.8		13.6-28.3	29.7 ± 2.8		23.5-35.6	
The incidence of sexual dysfunction, *n* (%)	62/70 (88.6)			7/70 (10)			
Proportion of patients with sexual dysfunction, M±SD	20.9±3.4		13.6-26.4	24.8±1.1		23.5-26.3	0.002*

* Changes are significant (p<0.05).

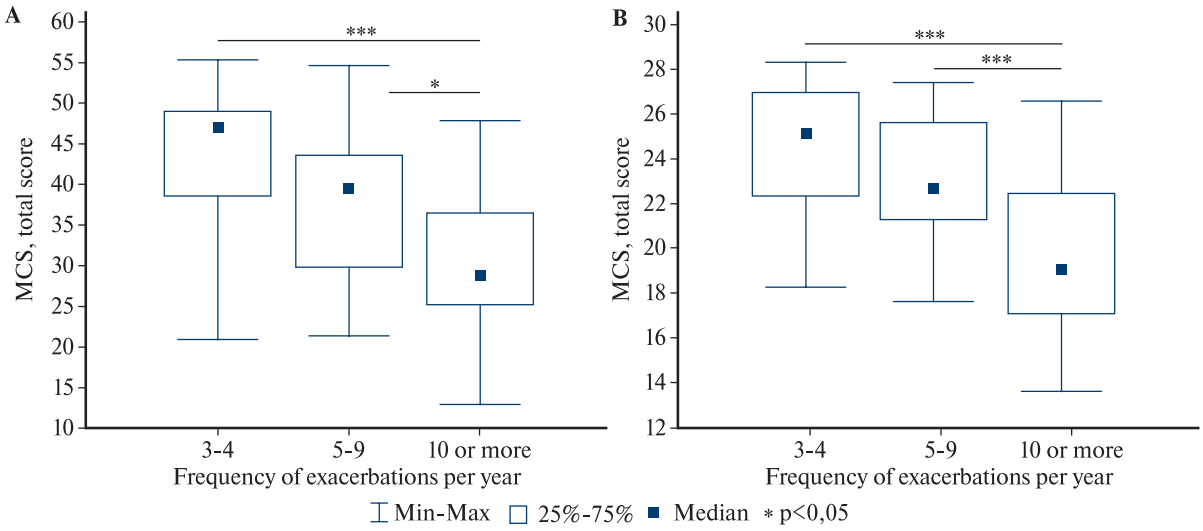

Fig. 2. Evaluation of the impact on the frequency of recurrences per year A) the mental component of the quality of life (MCS) B) the quality of sexual life (FSFI)

dysfunction persisted, the average total score was 24.76±1.1 compared to 20.59±2.87 (p=0.028) before treatment with the smallest increase in the orgasm domain (p=0.059).

Postoperatively, an increase in PCS domain score was observed in 82.9% of patients, MCS score improved among 90%, and total FSFI score in 97.1% of women. However, when comparing the total scores with the normative values, there was no effect of postcoital cystitis on PCS (p=0.06) with a strong effect on MCS (p<0.001). The correlation analysis revealed a weak inverse relationship between MCS, total FSFI score, and patient age. A moderate inverse relationship was found between the quality of sexual life and the duration of the disease (r = -0.34) (*fig. 1*). In addition, there was no relationship with the body mass index, as well as the influence of the described factors on PCS.

In the analysis of variance, the influence of age on the number of sexual intercourses was noted, however, in the post hoc comparison, the smallest difference was found between groups 1 and 3, but it was insignificant (p=0.05). When assessing the impact of the frequency of recurrences per year, the difference between groups 1 vs. 3 was seen (p<0.001); 2 and 3 (p=0.01) for MCS domain, as well as significant differences between the 1 vs. 3 and 2 vs. 3 groups (p<0.001) for total FSFI score (*fig. 2*). Analyzing the role of conservative (non-antibacterial) prevention methods, a significant difference was also noted in MCS domain and total FSFI score (p<0.001) (*fig. 3*).

Discussion. Despite the high prevalence of recurrent UTI, there are paucity of studies devoted to the impact on the quality of life. In addition, the impact of postcoital cystitis on the quality of life and sexual function has not been previously assessed [13]. Our study examined the

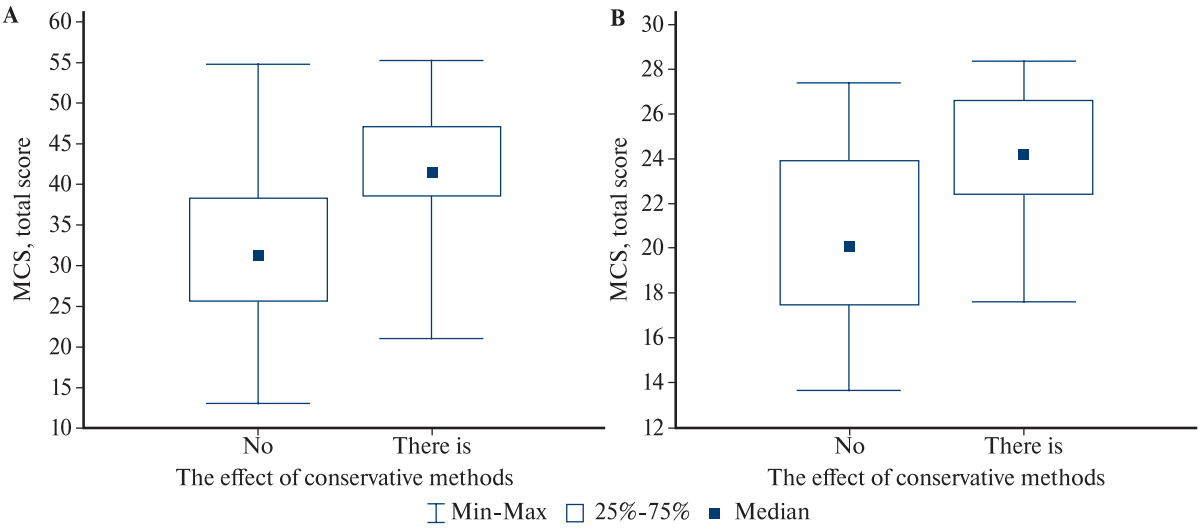

Fig. 3. Evaluation of the impact on the effect of conservative (non-antibacterial) methods of prevention A) the mental component of the quality of life (MCS) B) the quality of sexual life (FSFI)

impact of recurrent postcoital cystitis on quality of life and sexual function in women before and after urethral transposition. In line with published studies, we also indicate that recurrent UTIs have a significant impact on quality of life and sexual function.

Often, clinicians, when face with recurrent UTI, underestimate its social significance, as well as the degree of the impact on the quality of life, considering postcoital cystitis as a minor and easily treatable disease [17]. The GESPRIT study (2018), involving research centers in five European countries, including Russia, assessed the quality of life and economic costs in patients with recurrent UTIs, who had 3 or more recurrences per year. The authors noted that recurrent UTIs affect the daily activities and mental health of women in all European countries, and also have a significant impact on economic costs, which are reflected in increased number of days sick leave, doctor visits, and antibiotic prescriptions. As a result, they concluded: 1) patients are not satisfied with the efficiency of general preventive measures; 2) practitioners often recommend preventive measures only after multiple recurrences of UTIs; 3) women are often not informed about all possible methods of UTI prevention [13]. This study also showed the need for patients and healthcare workers to implement more effective strategies to prevent recurrent UTIs at earlier stage.

L. Boeri et al. demonstrated the impact of recurrent UTI on the sexual function (in average 5.29 episodes per year). The authors noted that all of the women were sexually active, and there was no association of recurrences of the cystitis with sexual intercourse. However, ⩾6 episodes of UTI per year had a correlation with FSFI score. Similar data on the effect of a number of episodes on total FSFI score were obtained in our study.

According to the literature, patients after various surgical interventions on the pelvic organs have sexual dysfunction, which negatively affects their quality of life. However, if sexual dysfunction is secondary, then methods for preventing recurrent postcoital cystitis, including urethral transposition, are an effective way to restore sexual activity, which is confirmed by the results of our study.

Conclusion. Recurrent postcoital cystitis has a significant negative impact on the quality of life and contributes to the development of severe sexual dysfunction. Our work emphasizes the social significance of the problem and confirms the high rehabilitation potential of extravaginal transposition of the urethra for the quality of life and sexual function.

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THE RESULTS OF THE MULTICENTER PROSPECTIVE COMPARATIVE STUDY OF ANDROGEL IN MEN WITH ENDOGENOUS TESTOSTERONE DEFICIENCY AND LOWER URINARY TRACT SYMPTOMS, ASSOCIATED WITH BENIGN PROSTATE HYPERPLASIA («POTOK»)

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Aim. To evaluate the efficacy and safety of using Androgel in men with endogenous testosterone deficiency and lower urinary tract symptoms (LUTS), associated with benign prostatic hyperplasia (BPH) in routine clinical practice.

Materials and methods. The multicenter, prospective, comparative study «POTOK» included 500 patients aged over 50 years with biochemical signs of testosterone deficiency (morning total testosterone concentration <12.1 nmol/l) and LUTS/BPH (International Prostatic Symptoms Score [IPSS] score of 8–19). The recruitment and monitoring of patients was carried out in 2022 in 40 clinics in Russia. Depending on the therapy, all patients were divided into two groups. The physician's decision to prescribe a specific drug (according to the approved patient information leaflet), as well as the subsequent follow-up scheme and therapy, was made a priori and independently of patient. In the first group (n=250) alpha-blockers and Androgel were prescribed, while in the second group (n=250) patients received monotherapy with alpha-blockers. The follow-up duration was 6 months. The efficiency of the therapy was evaluated after 3 and 6 months according to IPSS, symptoms of androgen deficiency (AMS and IIEF scores), uroflowmetry (peak flow rate, total urination volume), ultrasound study (postvoid residual and prostate volume). Safety was assessed by the total number of adverse events, stratified by severity and frequency. Statistical analysis was carried out using IBM SPSS 26.0.

Results. According to the primary end-point (IPSS score), there were significant differences between groups 1 and 2 after 3 months (11 vs. 12 points, p=0.009) and 6 months of therapy (9 vs. 11 points, p<0.001). There were also significant differences in the severity of symptoms of androgen deficiency after 3 and 6 months of therapy according to AMS score of 35 vs. 38 points (p<0.001) and 28 vs. 36 points (p<0.001), respectively. According to IIEF, all domains (erectile and orgasmic functions, libido, sexual satisfaction with and general satisfaction) were better in group 1 (p<0.001). After 6 months, uroflowmetry values also differed. In group 1 Qmax was 16 ml/s compared to 15.2 ml/s in group 2 (p=0.004); postvoid residual was 10 ml vs. 15.5 ml, respectively (p=0.001). The prostate volume in group 1 after 6 months of treatment was significantly lower (39.5 cc) compared with group 2 (43.3 cc; p=0.002). During the study, 18 mild AEs, 2 moderate AEs, and 1 severe AE were identified without significant differences between the groups (p>0.05).

Conclusion. The results of study «POTOK» showed greater efficacy and comparable safety of alpha-blockers in combination with Androgel compared with monotherapy with alpha-blockers in men with LUTS/BPH and endogenous testosterone deficiency in routine clinical practice. The increase in serum testosterone concentrations to normal values in patients with age-related hypogonadism favorably influence on the severity of LUTS and the potentiate the effect of the standard monotherapy with alpha-blockers.

Key words: *lower urinary tract symptoms (LUTS), benign prostatic hyperplasia (BPH), endogenous testosterone deficiency, Androgel.*

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Lower urinary tract symptoms (LUTS) are common in men, especially in the elderly [1, 2]. At the same time, benign prostatic hyperplasia (BPH) is a common cause of LUTS in this population [3, 4]. It is important to mention that the severity of LUTS may be associated not only with BPH and does not always correlate with prostate volume [5–7].

Based on current epidemiological data, it is known that approximately 25% of men in the population develop BPH/LUTS [8]. According to O.I. Apolikhin et al., more than 13 million men in Russia may suffer from BPH [9]. The prevalence of LUTS depends on the age, varying from 14% at 40–49 years to 40–60% or more at 60–69

years and later [10]. The importance of this problem is emphasized by the acceleration of rate of population aging, which is typical for Europe and America, as well as for Russia [11]. Therefore, an increase in the number of patients with BPH/LUTS is expected in the near future, making this problem even more important.

The current data on BPH are based on comprehensive basic researches. As a result of a number of studies, the concept of Isaacs and Coffey was formed, according to which, as a man becomes older, BPH goes through successive stages of micro- and macroscopic changes, which subsequently lead to clinical manifestations [11, 12]. The data of numerous publications show that the pathophysiological process of BPH development is multifactorial, and one of the main causes is changes in the hormonal levels with aging [13, 14].

The drug therapy for LUTS include alpha-blockers, 5-alpha-reductase inhibitors, type 5 phosphodiesterase inhibitors, much less often beta-3-adrenergic receptor agonists and antimuscarinics [15, 16]. According to the Canadian epidemiological study [17], alpha-blockers are prescribed most often (70%), 5-alpha-reductase inhibitors in 27% of cases, herbal medicine in 2%, and antimuscarinics only in 3% of cases. At the same time, monotherapy is used much more often than combination treatment (88 vs. 12%, respectively, $p<0.001$). In European countries, monotherapy with alpha-blockers is administered in 60-90% of patients, while 5-alpha-reductase inhibitors in 10-15% [18].

As already mentioned, the relative risk of LUTS with BPH increases with the age, which is also associated with the disturbance of endocrine function and the development of endogenous testosterone (T) deficiency with aging (age-related hypogonadism), which in turn requires appropriate and timely correction.

A number of pilot studies have shown that testosterone replacement therapy (TRT) has a positive effect on the severity LUTS in patients with age-related androgen deficiency [19–23]. There is a strong negative correlation between serum T (free and bioavailable) levels and the severity of LUTS, assessed by the International Prostate Symptom Score (IPSS). On this basis, a hypothesis suggested about the effect of T levels on the development and severity of LUTS. This effect of T and its metabolites can be explained by their action on alpha-adrenergic receptors, phosphodiesterase-5, the Rho-kinase system and endothelin, as well as nitric oxide synthase (NO-synthase), the effects of which are androgen-dependent [24].

NO-synthase has been extensively studied in men and proven to be present in the lower urinary tract. In addition, a number of studies have shown that its activity is the highest in the prostatic part of the urethra, in the bladder neck, and less in the detrusor [19, 20]. It is likely that nitric oxide may be one of the most important triggers in the relaxation of the bladder neck during urination [11]. The reproductive and urinary systems are interconnected embryonic and anatomically. T coordinates the activity of NO-synthase in the cavernous tissue, regulating the mechanism of erection through phosphodiesterase-5, and its action on the lower urinary tract can be explained in a similar way due to the presence of the same enzymes and androgen receptors [19, 20, 24].

In the case of endogenous androgen deficiency, it is necessary to administer TRT to recover T to normal values. This is considered an effective form of therapy for age-related hypogonadism and, therefore, treatment and prevention of associated conditions [11, 23, 25, 26]. Thus, the use of exogenous T preparations is justified in case of endogenous androgen deficiency in patients with LUTS/BPH.

The current observational study was carried out to obtain additional data on the efficacy and safety of Androgel®, a T gel for external use (Bezen Healthcare SA, Belgium), in men with endogenous androgen deficiency and LUTS/BPH.

Materials and methods. A multicenter prospective comparative non-interventional study "POTOK" was carried out to analyze observational data on patients over 50 years of age with biochemically-confirmed endogenous androgen deficiency (morning total T level <12.1 nmol/l) and LUTS (8–19 points on the IPSS) with BPH in routine clinical practice. This study was approved by the Interuniversity Ethics Committee (extract from the protocol No. 2 dated February 17, 2022). All procedures within the study were performed in strict accordance with the protocol and were routine, i.e., performed in the daily clinical practice of participating clinics, which determined the observational (non-interventional) nature of the study.

From February to June 2022, a total of 500 patients over the age of 50 were included in the study in 40 specialized clinics in Russia. Depending on the therapy received, all patients were divided into two groups. The physician's decision to prescribe specific drug (according to the approved instructions), as well as the tactics of further follow-up and treatment, was made independently before the inclusion of patient in the study. Patients of the first group (n=250) received alpha-blockers in combination with Androgel®, while in the second group (n=250) alpha-blockers without TRT was administered. The enrollment of patients in the study was carried out at medical centers in accordance with the criteria for inclusion and non-inclusion mentioned in the protocol.

Inclusion criteria:

- Men over 50 with biochemically-confirmed endogenous androgen deficiency (morning total T level <12.1 nmol/l);
- The presence of LUTS (8-19 points on the IPSS) with BPH (prostate volume> 25 cc);
- Presence of sexual activity or the desire to restore it;
- Physician's decision to prescribe α- blocker as monotherapy or in combination with Androgel® before the patient was included in the study;
- Willingness and ability of the patient to sign a written informed consent to participate in the study prior to enrollment.

Non-inclusion Criteria:

- Prostate cancer, surgical procedures during the study period;
- The occurrence during the study period of any diseases or conditions that worsen the patient's prognosis, and also preclude further participation;
- Study protocol violation, erroneous inclusion of a patient who does not meet the inclusion criteria and/or meets the non-inclusion criteria;
- Refusal of the patient to participate in the study;
- An adverse event (AE) requiring discontinuation of therapy.

Exclusion criteria:

- Contraindications to the use of α-blockers and/or Androgel® in accordance with the instructions;
- Any indications for surgical treatment of BPH;
- Lower urinary tract infections;
- Neurological diseases accompanied by LUTS;
- Patients previously enrolled in this study but withdrawn for any reason;
- Administration of α-blockers in less than 1 month and/or androgenic drugs in less than 6 months prior to inclusion in the study;
- Any clinical condition that, in the opinion of the investigator, is inconsistent with the inclusion criteria and may lead to early termination of the patient's participation in the study or make it difficult to interpret the results.

The follow-up of patients was carried out for 6 months. The inclusion visit was done on any day, which, in accordance with the routine clinical practice, was optimal for assessing the patient's condition and subsequent administration of appropriate therapy. After making a decision to prescribe alpha-blockers and Androgel® or alpha-blockers without TRT, the physician invited the patient to take part in the study by signing an informed consent. After assessing compliance with the inclusion and non-inclusion criteria, the patient underwent all the necessary procedures in accordance with the study protocol, and started to receive prescribed therapy. The type and dose of alpha-blockers were determined on an individual basis in accordance with routine clinical practice, medical standards and approved instructions. Follow-up visits 2 and 3 were carried at 3 and 6 months of therapy. At Visit 3, the patient completed participation in the study and was followed up by a physician in accordance with medical standards.

As part of the inclusion of the patient in the study, the following procedures were performed: collection of

Table 1

Anthropometric, demographic characteristics and medical history of patients

Parameter		Group 1 (*n*=250; alpha-blockers and Androgel)	Group 2 (*n*=250; alpha-AB without TRT)	*p*
Age (years)*		60 [55–66]	60 [55; 66]	0.978[1]
Height (cm)*		176 [174; 180]	177 [172; 180]	0.849[1]
Body mass (kg)*	Visit 1	96 [87; 102]	92 [85; 99]	**0.001[1]**
	Visit 2	93.75 [85.4; 99]	92 [84; 98]	0.124[1]
	Visit 3	91.15 [85; 97]	92 [84.6; 98.5]	0.798[1]
BMI (kg/m2)*	Visit 1	30.45 [27.78–33.24]	29.11 [26.81–31.71]	**0.001[1]**
	Visit 2	29.98 [27.23–32.37]	29.02 [26.57–31.56]	**0.046[1]**
	Visit 3	29.33 [26.85–31.52]	29.01 [26.83–31.64]	0.922[1]
Waist circumference (cm)*	Visit 1	103 [96–110]	100 [95–106]	**0.002[1]**
	Visit 2	100 [95–107]	100 [95–106]	0.501[1]
	Visit 3	98 [94–104]	100 [94–106]	0.069[1]
Hip circumference (cm)*	Visit 1	100 [92–110]	98 [90–105]	**0.027[1]**
	Visit 2	99 [92–108]	98 [90–105]	0.195[1]
	Visit 3	98 [91–105]	98 [90–105]	0.969[1]
Medical history				
19 [4–47]		11 [2–35.5]	0.0231	**0,023[1]**
18 [6–40.5]		14 [4–39]	0.1521	0,152[1]
Alpha-blockers (INN)**				
Alfuzosin		8.8%	11.6%	0.517[2]
Doxazosin		0.4%	1.2%	
Silodosin		13.6%	12%	
Tamsulosin		77.2%	75.2%	
Comorbidities**				
Hypertension		31.6%	23.6%	**0.045[2]**
Atherosclerosis		0.8%	0.8%	1.000[3]
Gastritis and gastroduodenitis		0.8%	2.8%	0.176[3]
Stomach ulcer		0.8%	0.4%	1.000[3]
Fatty liver disease		0.8%	1.2%	1.000[3]
Coronary artery disease		1.6%	2.8%	0.360[2]
Urolithiasis		1.6%	1.2%	1.000[3]
Insulin resistance		0.8%	2.0%	0.450[3]
Gout		0.4%	1.2%	0.623[3]
Diabetes mellitus		13.2%	8.0%	0.059[2]
Dyslipidemia		2.4%	0.8%	0.285[3]

* Me[Q1-Q3].
** proportion of patients from the study group, %
[1] Mann–Whitney U test for independent samples.
[2] Pearson's chi-square test.
[3] Fisher's exact test.

demographic and anthropometric data, taking a medical history; physical examination; assessment of the morning concentration of total T and total prostate specific antigen (PSA) in the serum, evaluation of LUTS severity according to the IPSS, androgen deficiency symptoms according to the Aging Males Symptoms (AMS) scale and erectile dysfunction based on the International Index Of Erectile Function (IIEF); ultrasound of the prostate; uroflowmetry (maximum flow rate [Qmax], voided volume); bladder ultrasound within 15 min after uroflowmetry (in order to determine postvoid residual [PVR]); assessment of concomitant therapy and AEs.

The main criterion for evaluating the efficiency (primary endpoint) of the therapy was the severity of LUTS according to the IPSS after 3 and 6 months of treatment. Secondary criteria (after 3 and 6 months of treatment) were change in symptoms according to the AMS and IIEF, uroflowmetry, prostate volume and PVR. Safety was assessed by the total number of AEs in patients, stratified by severity and frequency.

The exploratory and descriptive analysis of data was carried out using relevant statistical methods (parametric or nonparametric criteria for testing statistical hypotheses, taking into account the type and nature of the variables) using the IBM SPSS Statistics 26.0 program. When testing hypotheses (evaluation of differences between groups), a two-sided 5% significance level was used.

Results. The studied groups were heterogeneous in terms of a number of anthropometric and demographic data, as well as history of BPH (*Table 1*). At the time of inclusion in the study, the average body weight, body mass index (BMI), waist and hip circumference were significantly higher in group 1 compared to group 2 ($p<0.05$). However, there was a trend to the improvement of these parameters in group 1 after 3 and 6 months of therapy, which actually led to the equalization of the mean values between the groups (there were no significant differences at Visits 2 and 3; $p>0.05$). An analysis of BPH history showed a more prolonged duration of BPH/LUTS in patients of group 1 (19 [4–47] vs. 11 [2–35.5] months; $p<0.05$). However, age, height, LUTS, history of alpha-blockers taking and a number of concomitant diseases were similar in both groups ($p>0.05$).

At the start of the study, the mean total T level was significantly lower in group 1 compared to group 2 (9.13 vs. 9.80 nmol/l, respectively, $p<0.001$; see *figure*). However, during follow-up, T level significantly increased in group 1 and exceeded the value in group 2 after 3 months (13.6 vs. 10.10 nmol/l; $p<0.001$) and 6 months (16.0 vs. 10.10 nmol/l; $p<0.001$) of the treatment, which is associated with the effect of Androgel®. It should be noted that T level in group 2 did not change significantly during the follow-up.

Analysis of the prostate-specific antigen (PSA) level revealed no significant differences between two groups, both at the baseline (1.90 [1.26-2.80] vs. 1.96 [1.20-2.80] ng/ml; $p=0.373$), after 3 months (1.90 [1.40–2.50] vs. 1.90 [1.21–2.55] ng/mL; $p=0.968$) and 6 months of therapy (1.85 [1.40–2.40] vs. 1.90 [1.40–2.70] ng/ml; $p=0.363$), respectively. Therefore, it can be concluded that there was no effect of short-term TRT with Androgel® on PSA in patients with LUTS and BPH, which is also consistent with the findings of a previously published meta-analysis [27].

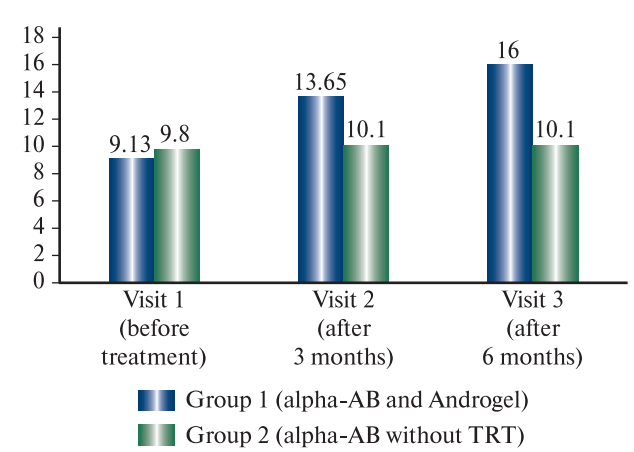

Fig. Average serum total testosterone level prior and during the treatment (nmol/l)

According to the primary endpoint for evaluating the efficiency (severity of LUTS as measured by IPSS), there was no difference between patients of two groups at baseline (15 [13–17] points in each group, p = 0.256; *Table 2*). However, significant differences were found after 3 months of therapy (11 [8–13] vs. 12 [9–15] points, respectively $p=0.009$), and after 6 months (9 [7–11] vs. 11 [7–14] points, respectively, $p<0.001$).

The average quality of life scores on Visit 1 and 2 were similar between groups ($p>0.05$), while on Visit 3 there was a significantly lower value in group 1 (2 [1–3] and 3 [2–3] points, respectively; $p<0.001$). According to the primary endpoint, a greater efficacy of therapy for LUTS/BPH with alpha-blockers and Androgel® compared with monotherapy with alpha-blockers was found. These data are consistent with aforementioned hypotheses about the potential of TRT to relieve LUTS in patients with hypogonadism and BPH [28–31].

According to the severity of symptoms of androgen deficiency, assessed by the AMS, there was no difference between patients of groups 1 and 2 at the beginning of the study (41 [36-48] vs. 41 [33-48] points, respectively, $p>0.05$; *Table 2*). However, a more significant decrease in group 1 compared to group 2 after 3 months (35 [28-39] vs. 38 [31-46] points, $p<0.001$) and 6 months (28 [24–35] vs. 36 [30–45], $p<0.001$) of therapy was seen. The results suggest the greater efficiency of combination therapy for LUTS/BPH with TRT using Androgel®.

Analysis of the IIEF scores showed that at baseline, patients in group 1 was either comparable to group 2 (domains "orgasmic function", "intercourse satisfaction"; $p> 0.05$), or had significantly lower values (domains "erectile function", "sexual desire", "overall satisfaction"; $p<0.05$; *Table 2*). The study of the changes with therapy showed that all domains of the IIEF were significantly higher after 3 and 6 months in group 1 compared to group 2. Therefore, patients who received Androgel® in the combination therapy of LUTS, had an advantage over monotherapy with alpha-blockers in terms of improving sexual function.

An analysis of uroflowmetry and ultrasound data (Qmax, voided volume and PVR) showed no significant differences between groups at baseline ($p>0.05$; *Table 3*). After 6 months of therapy in group 1, a higher Qmax and a lower PVR were found compared to those in group

Table 2

Parameters for evaluating the efficiency of therapy

Показатель		Group 1 (*n*=250; alpha-blockers and Androgel)	Group 2 (*n*=250; alpha-AB without TRT)	*p*
International Prostate Symptom Score (IPSS)				
Total score*	Visit 1	15 [13–17]	15 [13–17]	0.256[1]
	Visit 2	11 [8–13]	12 [9–15]	0.009[1]
	Visit 3	9 [7–11]	11 [7–14]	0.001[1]
Quality of life score*	Visit 1	4 [3–4]	4 [3–4]	0.155[1]
	Visit 2	3 [2–3]	3 [2–3]	0.513[1]
	Visit 3	2 [1–3]	3 [2–3]	0.001[1]
Aging Male Screening (AMS)				
Total score*	Visit 1	41 [36–48]	41 [33–48]	0.204[1]
	Visit 2	35 [28–39]	38 [31–46]	0.001[1]
	Visit 3	28 [24–35]	36 [30–45]	0.001[1]
The International Index Of Erectile Function (IIEF)				
Erectile function*	Visit 1	16 [12–20]	18 [12–22]	0.021[1]
	Visit 2	20 [15–23]	18 [12–22]	0.012[1]
	Visit 3	22 [16–25]	19 [12–22]	0.001[1]
Orgasmic Function*	Visit 1	6 [4–8]	6 [4–8]	0.049[1]
	Visit 2	7 [5–8]	6 [4–8]	0.001[1]
	Visit 3	8 [6–9]	6 [4–8]	0.001[1]
Sexual desire (libido)*	Visit 1	5 [4–6]	6 [4–6]	0.006[1]
	Visit 2	7 [6–8]	6 [4–7]	0.001[1]
	Visit 3	8 [6–9]	6 [4–7]	0.001[1]
Sexual Satisfaction*	Visit 1	7 [5–9]	7 [5–10]	0.341[1]
	Visit 2	9 [7–11]	7 [5–9]	0.001[1]
	Visit 3	10 [8–12]	7 [5–10]	0.001[1]
Overall Satisfaction*	Visit 1	4 [4– 6]	5 [4–7]	0.009[1]
	Visit 2	6 [5–8]	5 [4–7]	0.001[1]
	Visit 3	8 [6–9]	6 [4–7]	0.001[1]

* Me [Q1–Q3].
[1]Mann–Whitney U test for independent samples.

Table 3

Uroflowmetry and bladder ultrasound data

Показатель		Group 1 (*n*=250; alpha-blockers and Androgel)	Group 2 (*n*=250; alpha-AB without TRT)	*p*
Uroflowmetry values				
Qmax (ml/sec)*	Visit 1	12 [10–14.5]	12 [10–15]	0.917[1]
	Visit 2	15 [13–18]	15 [13–17.5]	0.565[1]
	Visit 3	16 [14.9–20]	15.2 [13–18]	0.004[1]
Voided volume (ml)*	Visit 1	249 [200–300]	250 [200–300]	0.612[1]
	Visit 2	258 [220–300]	251 [212–300]	0.418[1]
	Visit 3	280 [225–310]	260 [210–300]	0.059[1]
Bladder ultrasound (PVR)				
PVR (ml)*	Visit 1	37.5 [20.5–50.0]	37.0 [25.0–50.0]	0.572[1]
	Visit 2	20.0 [9.5–30.0]	20.0 [10.0–30.0]	0.143[1]
	Visit 3	10.0 [0.0–20.0]	15.5 [5.0–30.0]	0.001[1]
Prostate ultrasound				
Prostate volume (cc)*	Visit 1	43.9 [35.0–54.5]	44.4 [37.0–56.0]	0.169[1]
	Visit 3	39.5 [32.5–48.0]	43.3 [36.1–54.0]	0.002[1]

* Me [Q1–Q3].
[1]Mann–Whitney U test for independent samples.

Table 4

The severity of adverse events and their relationship with the treatment

Parameter		Group 1 (*n*=250; alpha-blockers and Androgel)	Group 2 (*n*=250; alpha-AB without TRT)	*p*
Severity of AE				
Severity of AEs	Mild	4	14	0.579[1]
	Moderate	1	1	
	Severe	0	1	
An association of AEs with the drug	Certain	0	2	0.594[1]
	Probable	1	1	
	Possible	1	1	
	Doubtful	2	5	
	Not classified	1	7	

[1]Pearson's chi-square test.

2: 16 [14.9–20] and 15.2 [13–18] ml/s (p=0.004), 10.0 [0.0-20.0] and 15.5 [5.0-30.0] ml, respectively (p=0.004).

Prostate volume assessed by ultrasound at baseline was 43.9 [35.0–54.5] and 44.4 [37.0–56.0] cc in groups 1 and 2, respectively (p> 0.05). After 6 months of treatment, there was a significant decrease in group of a combination therapy compared with group 2 (39.5 [32.5–48.0] and 43.3 [36.1–54.0] cc, respectively, p=0.002).

The relationship between T levels and prostate volume has long been controversial. However, the results of recent studies have shown an inverse correlation between these parameters. As a result, correction of age-related hypogonadism with TRT and the achievement of adequate T levels may reduce the inflammatory response in the prostate and decrease its volume, as well as the risk of BPH progression [32]. Our results are consistent with international data, which indicates the feasibility of using Androgel® in patients with endogenous androgen deficiency and LUTS/BPH.

During the study, 18 mild, 2 moderate, and 1 severe AE were documented without significant differences between the groups (p>0.05; *Table 4*). All AEs were in line with those described in the instructions for the medical use of drugs.

Discussion. Hypogonadism and BPH/LUTS are considered a logical and multi-stage manifestation of the aging process in men. However, due to the adverse effect on the quality of life and somatic health, special attention is paid to the study of these conditions. A lot of domestic and foreign publications are devoted to this topic and are consistent with results of our study "POTOK" [33–36]. It is clear that BPH and associated LUTS are frequently seen in patients with hypogonadism [33]. Although the strong correlation between these conditions is currently obvious, the pathogenetic mechanisms underlying it are still not fully understood [34], which requires further comprehensive researches.

At this stage of studying the hypogonadism, it is obvious that recovery of the serum T level with TRT to normal values in patients with BPH/LUTS provides significant clinical effects, assessed by a number of validated scales (IPSS, AMS, IIEF) and by uroflowmetry (Qmax and PVR) [33, 35, 36]. At the same time, the effect of T on the prostate remains to be controversial. Although in our study there is a significant decrease in the average prostate volume while receiving Androgel, in a previous work by A.A. Kamalov et al. [33] an increase in the prostate volume with the same duration of therapy was found. However, considering that a significant relationship between the intensity of prostate growth and T level has not been proven by a large number of previous studies, this question still remains unanswered. At the same time, the level of PSA did not change with TRT, both in our study and in a number of other works [35, 36]. Therefore, we confidently suggest the safety of the TRT with Androgel in patients with hypogonadism and BPH/LUTS.

The duration of TRT remains important question, whether it should be short-term or life-long treatment. Based on our results, it is obvious that at least 6 months is required before the efficiency of therapy can be assessed in terms of an improvement of urination. A number of previously works report that withdrawal of TRT leads to deterioration of symptoms to the baseline, while the resumption of therapy again results in their improvement [36]. Therefore, long-term or probably lifelong TRT in patients with age-related hypogonadism and BPH/LUTS should be considered, and requires further study in larger epidemiological studies with long follow-up.

Conclusion. The results of study «POTOK» showed greater efficacy and comparable safety of alpha-blockers in combination with Androgel compared with monotherapy with alpha-blockers in men with LUTS/BPH and endogenous androgen deficiency in routine clinical practice. The increase in serum T concentrations to normal values in patients with age-related hypogonadism favorably influence on the severity of LUTS and the potentiate the effect of the standard monotherapy with alpha-blockers. Considering time interval to improvement of LUTS and symptoms of T deficiency, combination therapy with alpha-blockers and T gel should be used for a long-term to achieve and maintain a beneficial effect.

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Attachment to the article. List of research centers and investigators

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9	Voronezh	MC "Cradle"	Koval Nikolai Alexandrovich
10	Moscow	SM Clinic	Kibets Sergey Anatolievich
11	Moscow	"Medicina"	Mkrtchyan Karen Gagikovich
12	Moscow	JSC "Medicina"	Belkin Andrey Ivanovich
13	Moscow	Miracle Doctor	Tsykin Daniil Sergeevich
14	Moscow	Clinic "Family Doctor	Butin Pavel Sergeevich
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MINIMALLY INVASIVE METHODS OF SURGICAL RECONSTRUCTION OF VESICOUTERINE FISTULAS

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Introduction. Vesicouterine fistula (VVF) is a rare disease. In 83-93% of cases it develops due to caesarean section. VVF is characterized by non-physiological communication between the bladder and the uterus. This disorder has a significant social impact, causing incontinence, persistent medical and psychological maladaptation. The gold standard for treating VVF is surgical reconstruction. Early and late results of minimally invasive approaches do not differ from open procedure, but only if the surgical team has sufficient experience.
Aim. To evaluate the efficiency of surgical treatment of VUF using a minimally invasive technique.
Materials and methods: From 2010 to 2021 a total of 15 patients with VVF were treated. The age of the patients varied from 18 to 37 years (mean 26.4 years). The average body mass index was 26.3 kg/m². The mean maximum fistula diameter was 10.7 mm (from 2 to 25 mm). The predominant cause of VVF was cesarean section (93%; n=14). In one case (7%), radiation-induced VVF was seen. Patients were randomized according to the Jóźwik and Jóźwik classification based on clinical manifestations. A type I of VVF was diagnosed in 4 patients (27%), type II in 9 patients (60%), type III in one woman. Recurrent urinary tract infection was observed in 53% (n=8) of cases. Four women were complaint of chronic pelvic pain syndrome (27%). The pain score on VAS did not exceed 6 points. All patients were undergone to minimally invasive procedures, including robot-assisted approach (n=5; 33%) and laparoscopic access (n=10; 67%).
Results. During the follow-up from 4 weeks to 10 years there was no recurrence of VVF. No indications for hysterectomy were found in any of the cases, however, it was carried out in two women after obtaining the informed consent. The average duration of robot-assisted procedure was 118 min (80–140), compared to 125.5 min (90–160) for laparoscopic access (p>0.05). The average length of stay after robotic procedure was 5.2 days (range 4 to 8 days) and 6.7 days (from 5 to 10 days; p> 0.05), respectively. Intraoperative blood loss did not exceed 130 ml. The mean value for laparoscopy was 97 ml, compared to 82 ml for robot-assisted approach (p>0.05). In both groups, there were no intra- and postoperative complications according to the Clavien-Dindo classification. Thus, there was no significant difference in the results of VVF closure between robot-assisted and laparoscopic approaches.
Conclusion. The results of minimally invasive surgical reconstruction of VVF do not differ from open procedure and depend on timely diagnosis, adherence to strict surgical techniques, and surgical experience, regardless of the approach.

K e y w o r d s: *vesicouterine fistula, urogenital fistulas, fistula reconstruction, laparoscopic, robot-assisted fistula reconstruction*

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Introduction. Vesicouterine fistulas (VUF) is a rare condition that is difficult to adequately diagnose and treat. Caesarean section (CS) is the cause of this disease in 83–93% of cases [1]. VUF more often develops with the lower segmental approach, and each subsequent CS increases the risk of developing the disease by 30% [2, 3]. It is noteworthy that since the XIX century by 1997, a total of 796 VUF were diagnosed worldwide, which confirms the limited number of observations and the lack of sufficient data for a meta-analysis and the development of accurate algorithms for diagnosing and treating this condition. In addition, most of the publications on the VUF presents clinical cases or an extremely small groups of patients [4, 5]. The rapidly growing number of women with VUF in recent decades is associated with an increase in indications and a number of CS performed.

The disease is characterized by non-physiological communication between the bladder and the body of uterus or cervix. It has not only pathognomonic manifestations, but also sufficient social impact, in some cases causing incontinence. In turn, it leads to persistent medical and psychological maladjustment of patients, severely affecting the quality of life, and may cause infertility [6]. Among all urogenital fistulas, VUF accounts for up to 1-16.4% of cases [7, 8].

This disease was first described by the prof. Youssef in 1957, therefore is often named as Youssef's syndrome. In the same work, the author described clinical manifestations of VUF, which are still relevant. The main complaint is cyclic menouria and amenorrhea. Prof. Youssef described the reason for the absence of urinary incontinence in these patients, which is associated with

a localization of the sphincter mechanism in the isthmus of the uterus [9]. It is worth noting that the mechanism of incontinence due to the communication between the bladder and the uterus body was described later, which basically has the features of the menstrual cycle. It has been established that for most of the cycle, intrauterine pressure is higher than intravesical pressure, which causes leakage of urine from the cervix. And only during a small part of the cycle the intravesical pressure becomes higher, therefore, a woman retains the urinary continence and physiologic urination for most of the time [10]. Frequent chronic genitourinary infections and the need for long courses of antibiotic therapy during recurrences are of great importance [11, 12].

In 2000, Jóźwik and Jóźwik proposed the first and, so far, the only classification of VUF, according to which all patients are divided into three groups based on clinical manifestations. Type I, characterized by the triad of amenorrhea, menouria and complete continence of urine has been known as Youssef's syndrome. Type II includes patients with cyclic menouria with regular menstruation and the presence of urinary incontinence, and type III VUF is associated urine leakage with normal vaginal menses and lack of menouria [13].

VUF is recognized as an iatrogenic fistula. To minimize the risks, it is necessary to know the causes of the development of the fistula during CS, which are described in detail and include [8, 14–17]:

1) Missed bladder rupture during an emergency CS. It often occurs at the onset of labor and is associated with incomplete bladder dissection and incomplete revision after delivery.
2) Unintentional stitching of the bladder wall when suturing the uterine wall.
3) Disruption of the blood supply to the bladder base, which develops as a result of many interventions and is more common in repeated CS.

Other causes of VUF described in the literature include prolonged labor, forceps delivery, vaginal delivery after a previous CS, manual removal of the placenta, use of a vacuum extractor, placenta previa, excision of a Gartner's cyst, radiotherapy, pelvic trauma, migration of the intrauterine device, anterior colporrhaphy, endometrial ablation, excision of necrotic uterine fibroids, tuberculosis, actinomycosis, and uterine damage by malignant tumor invasion [11, 18–21]. In one case VUF was associated with an abnormal development of the genitourinary system. The woman had a vaginal agenesis with cyclic menouria [22].

Patients with VUF have pathognomonic clinical manifestations, which in the vast majority includes cyclic presence of blood in the urine (menouria), less often accompanied by amenorrhea. If there are factors contributing to the difference in a pressure in the uterus and bladder, urinary incontinence also occurs. It is worth remembering that delayed development of symptoms, even 30 years after CS have been described [23].

Further verification of the VUF requires diagnostic examination. A cystoscopy with hysterosalpingography with the injection of a contrast agent has the highest specificity. This method allows to assess the location, size and axis of the fistula, as well as exclude an involvement of the ureteral orifices, which may require their simultaneous catheterization. A less specific, but reliable method is computed tomography (CT) or magnetic resonance imaging (MRI) cystography. It gives not only an information about a contrast extravasation into the uterine body/cervix with distended bladder, but also may delineate the anatomy of the urinary tract and anatomical landmarks to optimize surgical treatment, as well as exclude tumors in this area [8, 11, 24].

Conservative treatment of VUF is ineffective. Jóźwik and Jóźwik in their review described 41 cases of self-closure of VUF out of 796, representing a total of only 5.1%. The authors described the efficiency of conservative therapy in 28% of cases, but these results can be obtained, if only patients with a maximum fistula diameter of up to 2 mm are included. In addition, hormonal therapy is mandatory in order to achieve drug-induced amenorrhea ($p<0.001$) [4].

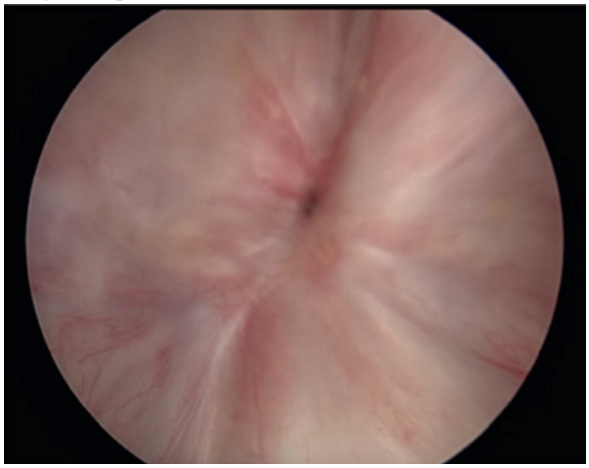
The gold standard for treating VUF is surgical reconstruction. In the absence of irradiation injury, the efficiency of VUF closure reaches 90%, regardless of approach. In addition, it is possible to perform simultaneous surgical procedures, hysterectomy, but only if there are clear indications. In women who desires to preserve a uterus, preventive hysterectomy should be refrained [24]. The best results of VUF closure can be achieved when surgical team includes urologists and gynecologists [25].

Early and delayed results of minimally invasive laparoscopic and robot-assisted reconstruction of VUF do not differ from open procedures, but only if the surgical team has sufficient experience. The advantages of laparoscopic and robot-assisted approaches are minimally invasive nature. They are associated with less intense pain syndrome, which in turn leads to a decrease in the use of narcotic analgesics, less blood loss with lower rate of blood transfusion, clear anatomical landmarks, allowing for more precise maneuvers, shorter length of stay, lower risk of wound complications and good cosmetic results. Disadvantages of this approach are expensive equipment, long learning curve, the need for extensive experience in minimally invasive procedures and the skill of intracorporeal suturing [26–28]. Single cases of transvaginal reconstruction of VUF are also described [29].

Aim. To evaluate the efficiency of surgical treatment of VUF using minimally invasive techniques.

Materials and methods. In the period from 2010 to 2021, in the GBUZ "Scientific Research Institute - Regional Clinical Hospital No. 1 named after. Professor S.V. Ochapovsky" the reconstruction of VUF was performed in 15 patients. The age varied from 18 to 37 years (mean 26.4 years). The mean body mass index was 26.3 kg/m^2. The maximum size of fistulous tract was 10.7 mm (from 2 to 25 mm). The predominant cause of VUF (93% of cases, n=14) was CS. In 2 (13%) patients VUF developed after primary CS, 33% (n=5) after second CS, and 7 (47%) women had three CS in a past history. Only in 1 (7%) case VUF was a result of irradiation damage. Patients were randomized according to the clinical manifestations, based on classification of Jóźwik and Jóźwik. Type I was diagnosed in 4 (27%) patients, type II in 9 (60%) patients, type III in 1 woman. Recurrent urinary tract infection was observed in 8 cases. Prior to surgery, all patients received antibiotic therapy, according to the urine culture. Chronic pelvic pain syndrome was observed in 4 (27%) patients. In this cohort, the pain syndrome was no more than 6 points on the visual analogue scale.

A. Cystoscopic view of the vesicouterine fistula



B. Efflux of indigo carmine, injected into the cervix, through a fistula into the bladder

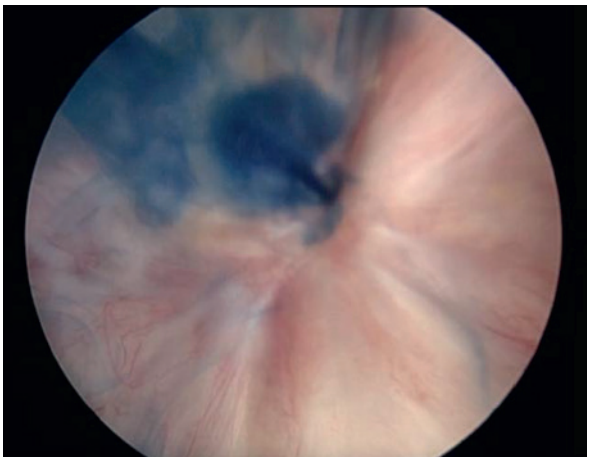


Fig. 1. Urethrocystoscopy and chromohysterography

The patients were fully examined. In all cases, VUF was verified by urethrocystoscopy and hysterography with an injection of indigo carmine 5% of 5 ml (*Fig. 1*). Under intravenous anesthesia and aseptic conditions, a urethral catheter 10-12 Ch was put in the cervical canal, through which 5.0 ml of a 5% solution of indigo carmine was injected and cystoscopy was simultaneously performed on a bladder volume of 200 ml. With the injection of indigo carmine into the uterine cavity, a leakage of dye appeared from the fistula. According to CT- or MR-cystography, extravasation of the contrast agent into the uterine cavity with overdistension of the bladder was seen in 12 (80%) cases (*Fig. 2*).

All patients underwent minimally invasive closure of VUF, including robot-assisted approach in 5 cases (33%) and laparoscopic approach in 10 women (67%). In both robotic and laparoscopic groups, trocars were placed at typical sites for pelvic procedures (*fig. 3*).

In all women there was a severe adhesive process in the abdominal cavity and pelvis. The first step was adhesiolysis. Next, the parietal peritoneum was cut in the projection of the vesicouterine pouch for a wide dissection of the anatomical structures (*Fig. 4*).

The mobilization of the bladder and the uterine wall was performed before visualization of VUF (*Fig. 5*). Further circular mobilization allowed wide excision of scar tissue.

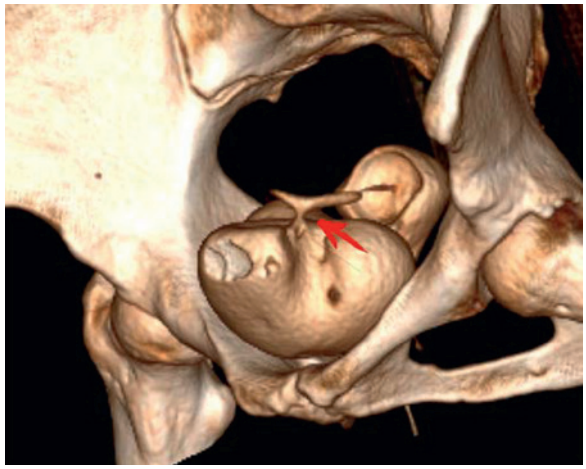


Fig. 2. Extravasation of the contrast agent on CT

In 13 cases, fistulas were located in the lower uterine segment, while in two cases in the cervix. For accurate identification of the lumen of the uterine cavity, a Hegar bougie was advanced into the cervical canal, which greatly facilitated the visualization of the localization and size of the fistula. After sufficient dissection of the bladder and uterus wall, excision of surrounding scar tissue was performed. Then, a stage-by-stage separate closure of the uterus and bladder defect was done with a two-layer continuous suture with a V-Loc 3/0 (*Fig. 6*). After the defect was closed, the bladder was checked for any leakage by injecting 200 ml of saline.

Regardless of an approach, all the principles of fistula closure were strictly followed. All procedures were performed using similar techniques. In 14 cases, it was possible to mobilize a flap of the greater omentum to wrap suture line and prevent a contact between viscera, which, in our opinion, is one of the fundamental aspects in preventing a recurrence (*Fig. 7*). Further, the irrigation of the abdominal cavity was carried out and drainage was put in the rectouterine pouch.

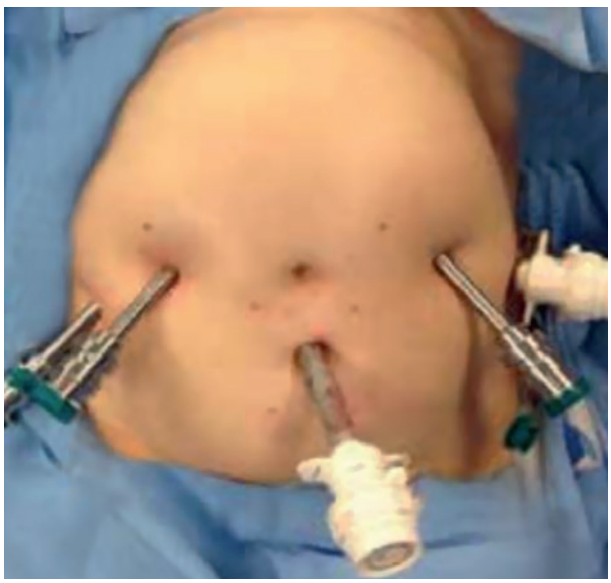


Fig. 3. Localization of trocars

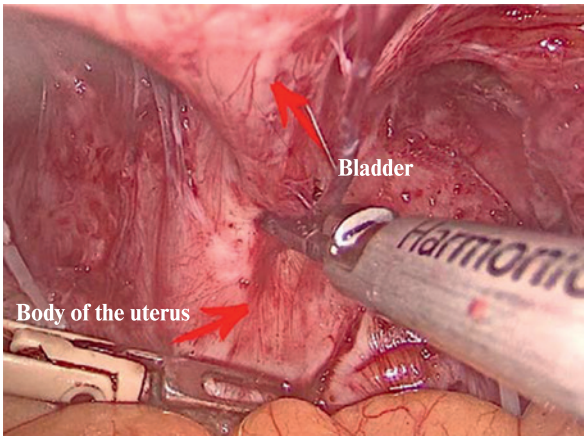


Fig. 4. Dissection of the bladder and body of the uterus

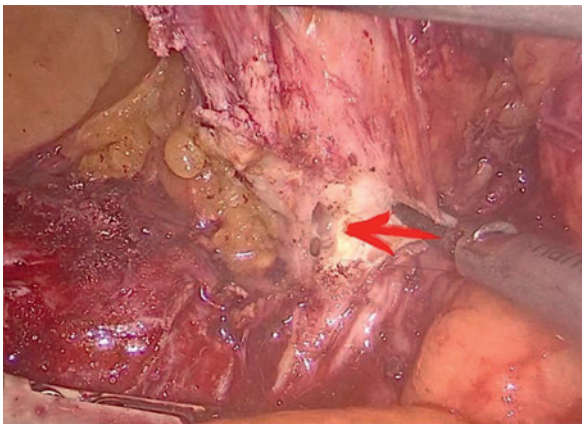
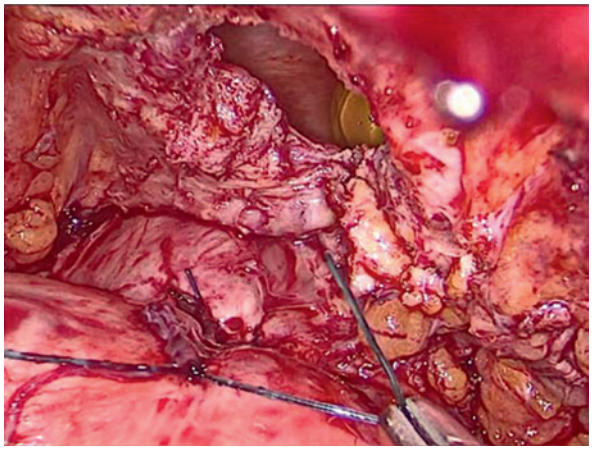


Fig. 5. Vesicouterine fistula

A. Suturing of the uterine wall



B. Suturing of the bladder wall

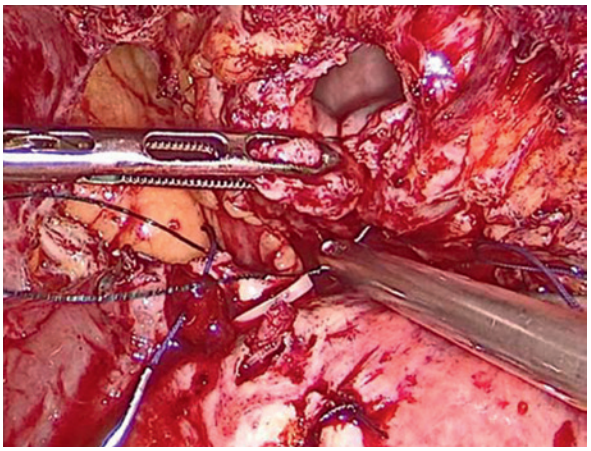


Fig. 6. Suturing of the bladder (A) and uterus (B) defects

Results. The evaluation of the results of surgical treatment was carried out with a consideration of the development of early and late recurrences, as well as the duration of the procedure, length of stay, the intensity of pain in the postoperative period, and the time of removal of the urethral catheter.

Of the 15 patients, there was no VUF relapse during the follow-up from 4 weeks to 10 years. The assessment

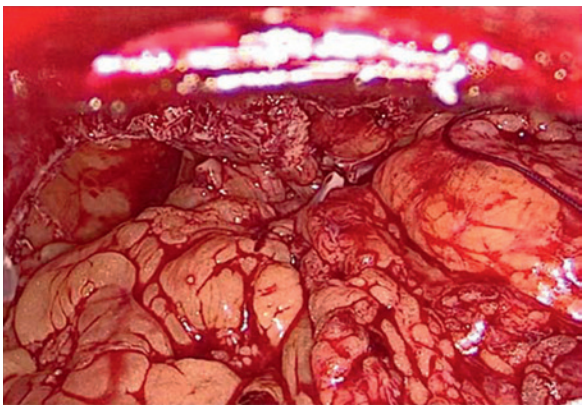


Fig. 7. Omental flap is advanced and fixed in the depth of vesicouterine space

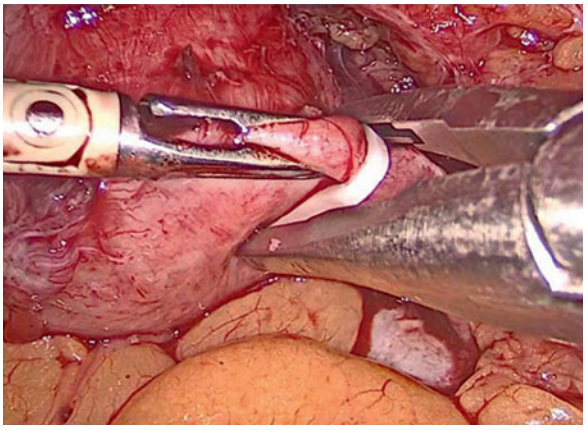


Fig. 8. Clipping of fallopian tubes

was carried out according to the restoration of cyclic menstruation, the absence of menouria and urinary incontinence (if it presented preoperatively), the water-tightness of the bladder during CT-cystography and a preservation of the uterus. It should be noted that no woman has any indications for hysterectomy. However, hysterectomy was done simultaneously in two cases in agreement with patients, since they had three children at the time of the procedure (*fig. 8*).

The average duration of a robot-assisted reconstruction was 118 minutes (from 80 to 140) compared to 125.5 minutes (100-160 minutes) with laparoscopic access ($p>0.05$). The average length of stay for robotic access was 5.2 days (range 4 to 8 days), for laparoscopic access 6.7 days (5 to 10 days); $p>0.05$. The intensity of pain syndrome was similar between two groups. Intraoperative blood loss in all 15 patients did not exceed 130 ml. For the laparoscopic approach it was in average 97 ml (50 to 130 ml), while for the robot-assisted approach 82 ml (30 to 110 ml); $p>0.05$.

Thus, the results of robot-assisted and laparoscopic reconstruction of VUF didn't significantly differ. In addition, there were no intraoperative and postoperative complications according to the Clavien–Dindo classification in both groups.

Discussion. One of the most important aspects of surgical treatment of VUF is the absence of recurrence and the possibility of preserving the uterus. Based on the few data in the literature, we have determined the prerequisites for successful fistula closure, including:

1. Meticulous adhesiolysis and dissection of the bladder wall and uterus.
2. Wide dissection of the layers.
3. Complete excision of scar tissue.
4. Double-layer repair of the uterus and bladder.
5. Tension-free suturing.
6. Water-tight closure.
7. Thin absorbable suture material.
8. Achieving complete hemostasis.
9. Use of a large omentum for wrapping suture lines.

It is important to remember that, despite all these rules, the main factor for a satisfactory surgical treatment of VUF is sufficient experience of the surgical team in laparoscopic and robotic procedures on the pelvic organs, including both transvesical and extravesical techniques of VUF closure. In our series, there was no significant difference in the results of fistula suturing between laparoscopic and robot-assisted approaches. As a consequence, the choice of approach should be determined only by the preference and experience of the surgeon.

After evaluating the results of VUF treatment by urogynecologists worldwide, we consider that a women should not plan pregnancy earlier than 2 years after reconstruction, however, the decision on the possibility of pregnancy is decided individually, taking into account specific features during the closure of VUF. According to different studies, the probability of pregnancy varies from 25 to 37.5% [8, 30].

In our study, all patients were undergone to reconstruction by a single surgeon in compliance with all the principles of fistula closure. Considering our results, we can suggest a direct correlation of the surgeon's experience with the absence of a recurrence of the VUF and the ability to preserve the uterus. The duration of the procedure largely depended on the severity of the adhesions in the abdominal cavity and pelvis, as well as on the extent of fibrotic process and the different lengths of the intracorporeal sutures of the uterus and bladder.

Conclusion. The results of minimally invasive laparoscopic reconstruction of VUF do not differ from open approach and directly depend on timely diagnosis and surgical treatment, adequate preoperative patient's preparation, taking into account the intraoperative features of fistula closure and the experience of the surgeon, regardless of the access. It is necessary to preserve the uterus, if there is no absolute indication for hysterectomy, and offer hysterectomy in case of high risks of VUF recurrence during a pregnancy.

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THE ROLE OF ELECTRON MICROSCOPY OF EJACULATE IN THE DIAGNOSIS OF INFERTILITY ASSOCIATED WITH HUMAN PAPILLOMAVIRUS INFECTION

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Introduction. The problem of male infertility is multifactorial. However, in recent years, the question of the involvement of viruses, in particular human papillomaviruses (HPV), in the development of this condition has been actively discussed.
Purpose of the study. To study the role of ejaculate electron microscopy in the diagnosis of infertility associated with human papillomavirus infection.
Materials and methods: The analysis of the results of electron microscopic examination of the ejaculate in 51 patients aged 22 to 40 years (mean age 32.3 ± 6.4) with a diagnosis of infertility and pathospermia, combined with human papillomavirus infection (PVI), but with the absence of other risk factors, was carried out.
Results: Various variants of pathozoospermia were found in the ejaculate: asthenozoospermia (35.3%), asthenoteratazoospermia (31.4%), oligoasthenoteratazoospermia (19.6%), oligoasthenozoospermia (13.7%). Among the studied HPV types of high oncogenic risk prevailed (16, 18). More often (88.2%), HPV was registered as part of associations with dominance of types 16 and/or 18 and 33, as well as types 18 and 33. In electron microscopy, in 80.3% of cases, HPV was fixed on spermatozoa with localization on the acrosome (76.4%) and in the sperm plasma (52.9%).
Conclusions: PVI, regardless of the type of HPV and the localization of virions on spermatozoa, significantly impairs the progressive motility and morphology of spermatozoa. The electron microscopy method allows not only to detect HPV in the ejaculate, but also to clarify its localization on the spermatozoon and determine those negative changes in the spermatozoon that are caused by the virus.

K e y w o r d s: *Infertility, human papillomavirus, ejaculate, spermatozoa*

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Introduction. Currently, the problem of infertility affects about 15% of married couples in the world, while every eighth couple faces it when planning the first child [1-3]. In half of childless couples, infertility is associated with the male factor manifested by various types of pathospermia [4]. The problem of male infertility is multifactorial [2, 5]. In recent years, the involvement of viruses, in particular the human papillomavirus (HPV), in the development of the infertility has been actively studied [6, 7].

HPV-associated diseases are more often sexually transmitted [7, 8]. Currently, more than 200 different HPV genotypes are known, which were divided into low or high-risk types according to oncogenic potential [9–11].

For many years it was believed that low-risk HPV was involved in various diseases of the skin and mucous membranes, while high-risk HPV was associated with oncological diseases of the urinary tract and reproductive organs in both men and women [12]. In most cases, HPV is eliminated by the immune system within 12–24 months without any clinical manifestations. At the same time, the inability of the immune system to eliminate the virus leads to the persistent viral infection and causes a number of conditions, which were mentioned above [12, 13].

However, a recent study by G. Capra et al. (2022) [13] indicated that both high and low-risk types of HPV are involved in the development of inflammatory diseases of the urethra, bladder, prostate, and testicles. Also, HPV (especially high-risk group) can affect the reproductive health and fertility of both women and men and the couple as a whole [13, 14].

HPV infection contributes to the development of adverse pathological conditions, including a decrease in male fertility, characterized by qualitative and quantitative changes in the ejaculate, impaired couple fertility with increased apoptosis of blastocyst and decreased implantation of trophoblastic cells into the endometrium, malformations of embryos and fetuses with an increase in the number of spontaneous abortions and spontaneous premature births [14].

In recent years, there have been some studies devoted to the mechanisms of negative influence of HPV in men on the sperm quality and pregnancy outcomes. However, data on this issue are scarce and contradictory. It is known that HPV has a direct pathogenic effect, causing genetic instability/DNA damage in spermatozoa, as well as inhibits the immunocompetent component of the reproductive system, activating autoimmune processes in the testicles, including the synthesis of

cytokines, as a result of which spermatogenesis is affected [15].

Therefore, it is necessary not only to detect the virus in the ejaculate, but also to study their negative impact on spermatozoa.

Aim. To study the role of electron microscopy of ejaculate in the diagnosis of infertility associated with HPV.

Materials and methods. The analysis of the results of electron microscopy of the ejaculate in 51 patients aged 22 to 40 years (mean age 32.3 ± 6.4 years) with a diagnosis of infertility and pathospermia, combined with HPV, who had no other risk factors, was carried out.

Inclusion criteria were age over 18 years, the diagnosis of infertility (an inability of a healthy partner to become pregnant within 1 year with regular sex without contraception), a positive result of polymerase chain reaction (PCR) for HPV, consent of patients to participate in the study.

Exclusion criteria: other sexually transmitted diseases, infectious and inflammatory diseases of the reproductive organs of bacterial etiology (prostatitis, vesiculitis, orchitis, urethritis), bladder outlet obstruction (urethral stricture, neurogenic dysfunction of the lower urinary tract, etc.), concomitant cardiovascular, neurological, endocrine, systemic and other diseases, malignant tumors at present or in history, hormonal disorders of the reproductive system, urogenital malformations, and immunodeficiency state.

A study of the ejaculate was performed. Ejaculate samples were collected in a special sterile container by masturbation after the recommended period of sexual abstinence for 3–4 days, taking into account all recommendations for a preparation. After liquefaction at room temperature, the concentration, motility and normal morphology of spermatozoa were assessed in accordance with the recommendations of the World Health Organization for semen analysis (2010). An aliquot of the sperm of each patient was sent to the clinical and morphological laboratories.

For electron microscopy, native ejaculate was fixed in 2.5% glutaraldehyde (AppliChem, Germany) for 24 hours. After fixation, the material was washed three times (for 15 min) in phosphate buffer. After processing in buffers, the slides were placed in a 1% OsO4 solution (Acros Organics, Belgium) in a phosphate buffer pH 7.2–7.4 for 1.5 hours, then dehydrated in ascending concentrations of alcohol and acetone, and embedded in epoxy resin Epon-812 by the plane-parallel method and polymerized at 600. The resulting epoxy resin blocks were turned on a high-speed Leica EM TRIM cutter to obtain semi-thin sections stained with toluidine blue. The glomeruli were further searched for. Epoxy resin blocks containing glomeruli were cut using a diamond knife on an Ultracut-UC6 ultramicrotome (Leica, Germany). The thickness of ultrathin sections was 70 nm.

A contrasting of the sections was performed using a 1.5% solution of uranyl acetate in 700 ethanol and lead citrate. After contrasting, the sections were viewed in a Jem 1011 transmission electron microscope (Jeol, Japan) with an Erlangshen ES500W digital camera (Gatan, USA, Canada). The dimensions of ultrastructures were measured in absolute units (μm and nm). If necessary, ultrastructure morphometry was done using DigitalMicrograph software (Gatan, USA). The amplification method of PCR DNA diagnostics was used to identify the type of virus. The analysis covered all currently known high-risk types (HPV-16, HPV-18, HPV-26, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-53, HPV-56, HPV-58, HPV-59, HPV-64, HPV-66, HPV-67, HPV-68, HPV-69, HPV-70. HPV-73, HPV- 82), and low-risk types (HPV-6, HPV-11, HPV-40. HPV-42, HPV-43, HPV-44, HPV-54, HPV-55, HPV-61, HPV-62, HPV-71, HPV-72, HPV-81, HPV-83, HPV-84, HPV-87, HPV-89, HPV-90). The distinction between high and low-risk HPV types was based on the International Agency for Research on Cancer classification using PCR technique.

For statistical analysis, the obtained data were entered into Microsoft Excel spreadsheets of the Microsoft Office

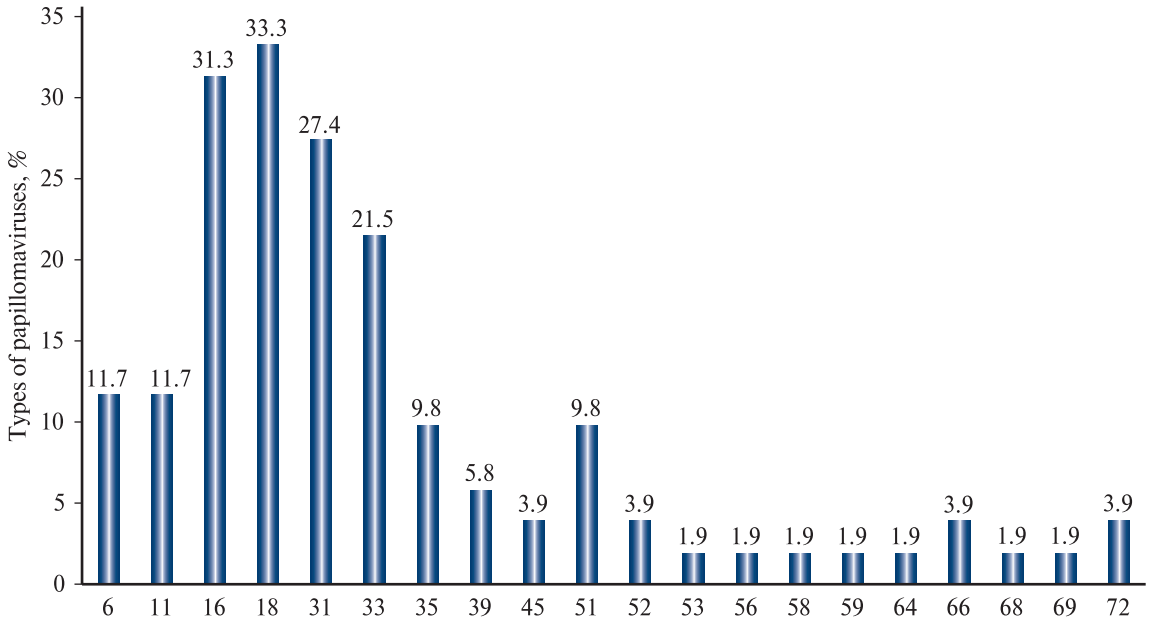

Fig. 1. Types of papillomaviruses detected in ejaculate

2007 software package. Then, the STATISTICA 6.1 software package was used (StatSoftInc, USA). The calculations and interpretation of the results were carried out according to the guidance of O.Yu. Rebrova.

The study was carried out on the basis of the urological clinic of the FGBU VO "RostGMU" and LLC Medical Center "Professional" as part of the thesis "Assessment of the human papillomavirus in male infertility", approved by the Local Independent Ethics Committee of the FGBU VO "RostGMU", protocol 16/19 dated 10/17/2019.

Results. When analyzing the ejaculate, asthenozoospermia (35.3%) and asthenoteratazoospermia (31.4%) were more commonly detected. The proportion of oligoasthenoteratazoospermia and oligoasthenozoospermia was 19.6 and 13.7%, respectively.

In all the patients, various HPV types were detected in the ejaculate. Moreover, out of 20 identified viruses, 17 (85.0%) belonged to high-risk group (*Fig. 1*). Among HPV types, 18 (33.3%) and 16 (31.3%) were predominated. HPV of 31 and 33 types were detected less frequently (27.4% and 21.5%, respectively). The proportion of other viruses was significantly lower ($p<0.05$). Interestingly, in 88.2% of cases, associations of several types of HPV were recorded in the ejaculate with the dominance of the 16 and/or 18 and 33 types, as well as the 18 and 33 types.

It should be noted that in all patients with oligoasthenoteratazoospermia, three types of HPV were detected in the ejaculate: 16, 31, and 33.

A negative impact of HPV on the morphological characteristics of spermatozoa remains poorly understood, however, the virus can be present in various semen fractions. In this case, the pathogenic potential of the virus can be directed to various components of both the spermatozoon and the ejaculate. When analyzing the results of electron microscopy, fixation of the virus on spermatozoa was noted in 80.3% of patients. At the same time, in the majority (76.4%) of men, the virus was localized on the acrosome, and in 52.9% of cases it was detected in the semen plasma (epithelial cells, etc.) (*Fig. 2, 3*).

In addition, when performing an electron microscopy of the ejaculate, various pathological changes in the sperm cells were revealed with predominance (76.4%) of acrosome changes (*Fig. 4*).

It has now been established that acrosome changes in most cases is a fundamental factor in reducing the fertility potential. In the studied cohort, various changes in the acrosome were detected, including a dilation of the subacrosomal space (52.9%), reduced size of the acrosome (43.1%) and pathological changes in the post-acrosomal region (33.3%) (*Fig. 5*). In addition, the majority (60.8%) of the patients had pathological changes in the nucleus: the presence of non-condensed (29.4%) and damaged chromatin (31.4%), and the abundance of vacuoles was noted in 27.4% of patients. The most severe changes in the acrosome were detected in the presence of the 31 and 33 types of HPV in the ejaculate.

Discussion. In recent years, there has been increasing interest in the health community to explore how HPV

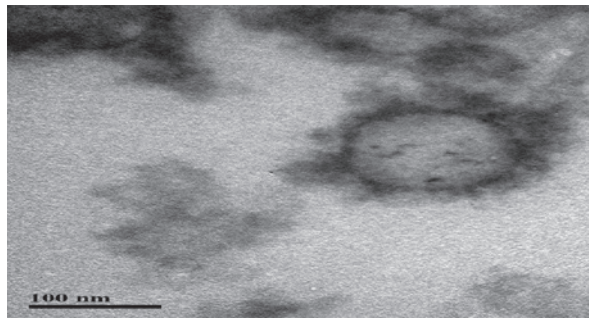

Fig. 2. Localization of viral capsid on the acrosome

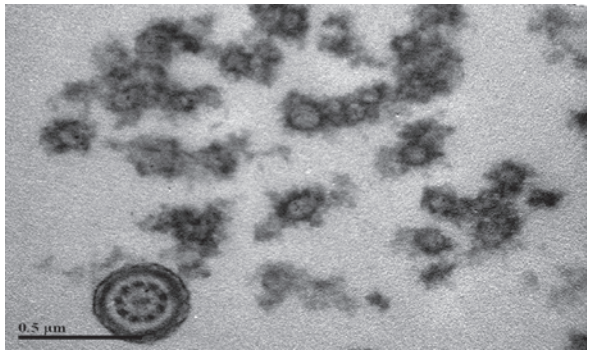

Fig. 3. Localization of viral capsid in the epithelial cells in semen plasma

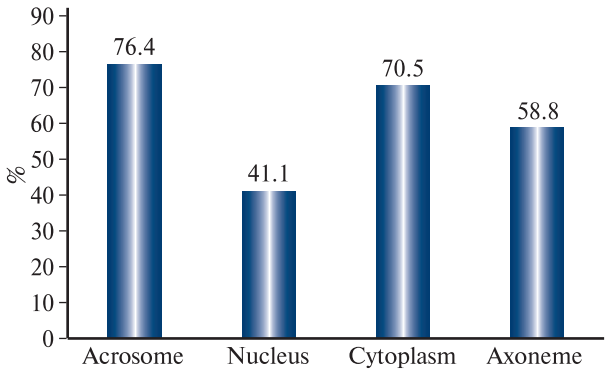

Fig. 4. The structures of spermatozoa most often damaged by HPV

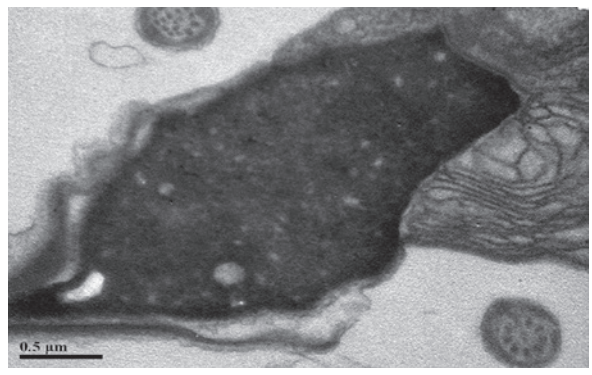

Fig. 5. Abnormal deformed acrosome

infection in men can contribute to poor sperm quality and negative pregnancy outcomes. However, opinions are contradictory and far from consensus.

The structure of HPV types presented in our study partially corresponds to the results of previous publications, in which it was found that high-risk types (16, 18, 31, 33) are more often detected in infertile men. The combined effect of various pathogenicity factors, as well as the persistence of the virus, contribute to the long-term presence of HPV, causing various types of pathospermia [15].

The studies of Y. Kato et al. (2021) and A. Piroozmand et al. (2020) showed that HPV-positive patients had low proportion of sperms with progressive motility and a high percentage of immobile spermatozoa [18, 19]. A number of authors [19, 20], when studying the qualitative ejaculate parameters, found that in HPV-positive semen samples of both fertile and infertile patients, the number of spermatozoa with normal morphology decreases. This is consistent with the results of our study.

Pathospermia associated with HPV may be due to the presence of the virion in any component of the ejaculate. According to electron microscopy, we have identified various variants of both acrosomes and axonemes of spermatozoa, which led to qualitative and quantitative changes in the characteristics of the ejaculate. In addition, it has been found that spermatozoa, somatic cells and seme, plasma may contain different types of HPV.

An important point of our study was the use of the electron microscopy, which allows to identify the exact localization of the virus, and resulting pathological changes in the sperm cells. In most patients, pathological changes in the sperm acrosome were detected. At the same time, the most frequent point of HPV adhesion is the post-acrosomal region, which is an important factor in the activation of oocytes. In addition, this structure is one of the determining factors in the penetrating ability of spermatozoa, which can only be detected by electron microscopy. In most patients, there was a decrease in the integrity of the post-acrosomal region and a dilation of the subacrosomal space.

These changes are crucial when planning pregnancy, as well as when proceeding with assisted reproductive technologies.

Conclusions. Based on our previous data and the results of the present study, it can be concluded that HPV, regardless of the type and localization of virions on spermatozoa, significantly impairs progressive spermatozoa motility and morphology. The method of electron microscopy allows not only to detect HPV in the ejaculate, but also to clarify its localization on the sperm cells, to determine those negative changes in sperm cells that are caused by the virus.

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PEFFICACY OF FESOTERODINE FOR PREVENTION OF AUTONOMIC DYSREFLEXIA IN PATIENTS WITH NEUROGENIC DYSFUNCTION OF THE BLADDER AFTER SPINAL CORD INJURY

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Aim: to evaluate the effectiveness of fesoterodine for the prevention of autonomic dysreflexia (AD) in patients with neurogenic bladder dysfunction (NBD) after spinal cord injury (SCI).
Materials and methods: a total of 53 patients with AD were included in the study. In the main group (n=33) patients received fesoterodine 4 mg per day for 12 weeks as a treatment for neurogenic bladder dysfunction and prevention of AD. In the control group (n=20), patients were monitored for 12 weeks without specific treatment. The assessment was based on the results of ADFSCI and NBSS questionnaires, daily blood pressure monitoring with the completion of a self-observation diary, cystometry with simultaneous monitoring of blood pressure and heart rate.
Results: In the main group there was a significant decrease in episodes and severity of AD according to ADFSCI questionnaire and an improvement in the quality of life according to NBSS questionnaire compared to the control group ($p<0.001$). Also, in the main group, the number of episodes of AD and systolic blood pressure decreased. The maximum bladder capacity and bladder compliance increased ($p<0.001$), and the maximum detrusor pressure and systolic blood pressure when the cystometric capacity was reached, decreased significantly ($p<0.001$) in the main group compared in comparison with the control group.
Conclusion: Fesoterodine at a dosage of 4 mg for 12 weeks reduced the severity of symptoms of AD in patients with SCI and NBD, which was manifested by the stabilization of blood pressure and a decrease in the number of episodes of AD, which significantly improved the quality of life. Also, the drug led to a significant improvement in urodynamic parameters during cystometry, in the form of a decrease in detrusor pressure and an increase in cystometric capacity. We can conclude that fesoterodine is effective in the prevention of AD in patients with NBD after SCI.

K e y w o r d s: *autonomic dysreflexia, fesoterodine, neurogenic bladder dysfunction, spinal cord injury*

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Introduction. Autonomic dysreflexia (AD) is a medical emergency characterized by sudden and excessive activation of the autonomic nervous system in patients with spinal cord injury (SCI) at or above the T6 due to irritant stimuli below this level. Common causes of AD are neurogenic detrusor overactivity (NDO), bladder overdistention (75–85% of cases), renal colic, rectal distension, too-tight clothing, ingrown toenails, and bone fractures [1, 2]. Clinically, AD is manifested by a sudden onset of severe throbbing headache. Piloerection, crawling sensation, redness and sweating above the level of SCI along with blurred vision and nasal congestion are also possible [2].

The European Association of Urology defines AD as a condition characterized by an increase in systolic blood pressure (SBP) above baseline by 20 mm Hg. Mean baseline BP in patients with a high level of spinal cord injury is significantly lower than in the general population [3]. An increase in BP in this cohort of patients can lead to serious cardiovascular complications, such as myocardial infarction, cerebral hemorrhage, convulsions, pulmonary edema, and retinal detachment [4]. Also, AD significantly worsens the quality of life and the process of rehabilitation of patients with SCI.

The prevalence of AD and the frequency of its episodes are often underestimated. In the study of E. Lee and M. Joo, 26 (92.9%) of 28 patients with SCI above the T6 with daily monitoring of blood pressure had from 1 to 10 episodes of AD per day [5]. Despite the exact review of AD in the United States of America, its prevalence rates vary significantly and reaches 48-90% of all individuals with SCI above the T6. Patients with complete SCI have a much higher incidence of AD (91% with complete SCI versus 27% with incomplete SCI) [6].

There are no major epidemiological studies in the Russian Federation on AD, despite the fact that the

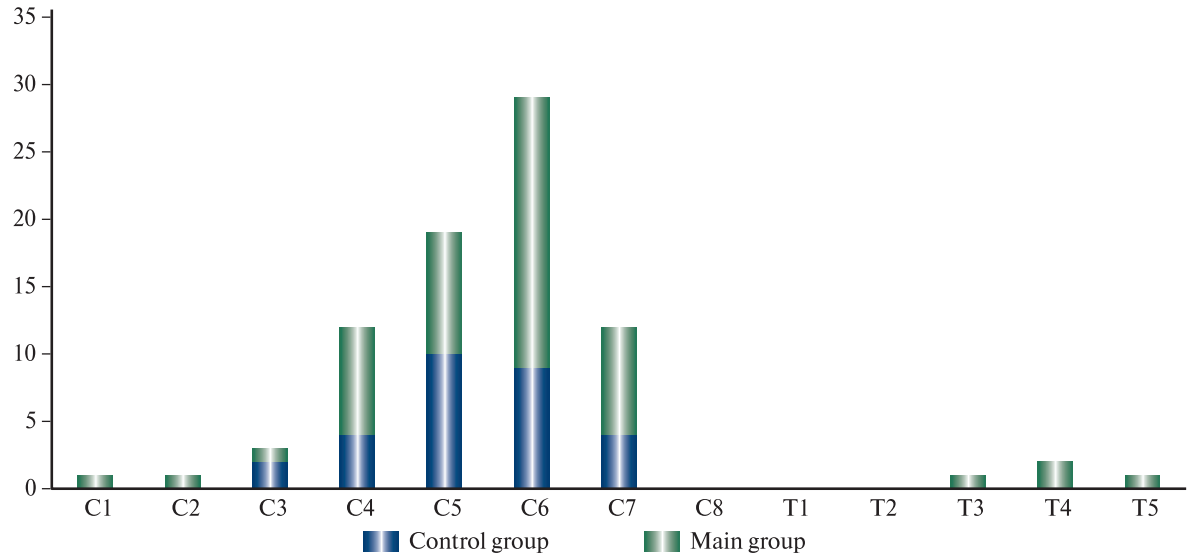

Fig. 1. The level of damage to spinal cord segments in patients in the main and control groups

number of people with SCI has increased 200 times over the past 70 years. More than 8,000 new cases in Russia occurs every year [7].

To date, methods for the treatment and prevention of AD are limited. In the literature, data on the efficiency of such drugs as nifedipine [8], angiotensin-converting enzyme inhibitors, baclofen [9], alpha-blockers [10], as well as injections of botulinum toxin into the detrusor are presented [11]. Antimuscarinics are one of the promising directions in the prevention of AD. M. Virseda-Chamorro et al. described their experience in the treatment of AD with fesoterodine [12]. A phase 2, open-label, non-randomized, single-center study has been launched to evaluate the effect of fesoterodine on the incidence and severity of AD in patients with SCI above the T6 [13]. The molecular structure of the drug prevents its penetration through the blood-brain barrier, reducing central nervous system (CNS) side effects compared to other antimuscarinic drugs such as darifenacin, solifenacin, tolterodine, oxybutynin [14].

Aim. To evaluate the efficiency of fesoterodine for the prevention of AD in patients with neurogenic detrusor overactivity (NDO).

Materials and methods. A total of 53 patients with SCI above the T6 (7 women and 46 men) were included in the study. The work was carried out on the basis of the Medical Scientific and Educational Center of Moscow State University named after M.V. Lomonosov and the rehabilitation center for the disabled "Overcoming" from 2019 to 2022. The study design was approved by the local independent ethics committee of the Medical Scientific and Educational Center of Moscow State University named after M.V. Lomonosov (minutes No. 2/21 dated February 8, 2021). All patients or their legal representatives signed a voluntary informed consent prior to the inclusion in the study.

The baseline condition of all 53 patients was evaluated using the ADFSCI (questionnaire for a preliminary assessment of the frequency and severity of manifestations of AD) and quality of life domain of the NBSS questionnaire. In addition, a determination of baseline blood pressure, ABPM, filling cystometry with simultaneous monitoring of blood pressure and heart rate were also done. Urodynamic study is considered as one of the most accurate methods for confirmation of the association of AD with neurogenic bladder dysfunction [2]. All patients were divided into two groups. A follow-up survey using the ADFSCI and NBSS questionnaires was carried out every 4 weeks during a period of 12 weeks. A complete examination was performed once again at the end of 12 weeks. In the control group (n=20), patients did not receive any drugs that affects the functional state of the lower urinary tract during 12 weeks.

This study was carried out in accordance with the Declaration of Helsinki (revised in Fortaleza, Brazil, October 2013). Data collection and statistical analysis was carried out using MS Excel, 2016, JASP v.0.16.3 software (University of Amsterdam, Amsterdam, Netherlands, 2022). Data of quantitative variables are presented in the form of tables, including mean, median, standard deviation, minimum, maximum, Q1 and Q3 values. For the analysis of quantitative variables in related groups, the Wilcoxon test or test of Friedman were used, and the exact value of the probability of error of the first kind (p-value) was given. Also, for the test of Friedman, the results of the post-hoc test, adjusted according to Bonferroni and Holm, were presented. The results were considered significant if $p<0.05$. The visualization of quantitative variables was carried out using box plot and raincloud plots. Categorical variables are presented with bar charts.

Results. There were no gender differences between main and control groups (p=0.18; Fisher's exact test). The mean age of patients in the main group was 35.2±8.8 years, in the control group 42.3±10.7 years (difference was significant; p=0.019, Mann-Whitney U-test). In the control group, SCI occurred on average 10.5±6.8 years ago (minimum 2 years, maximum 26 years) compared to 8.6±6.1 years in the main group (minimum 1 year, maximum 21 years); differences were insignificant (p=0.33, Mann–Whitney U-test). The level of SCI is presented in *fig. 1*.

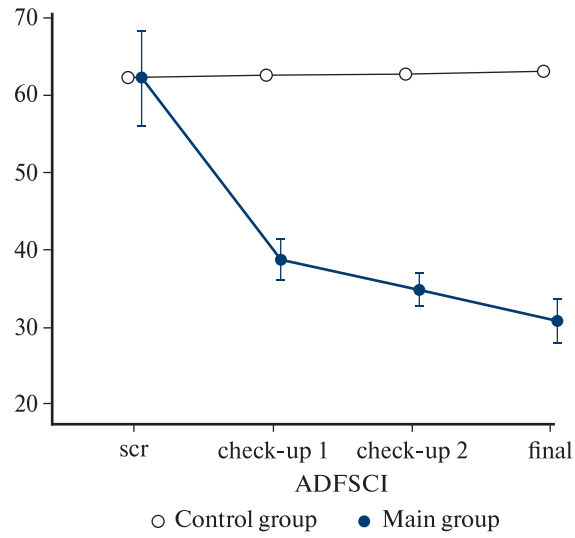

Fig. 2. Dynamics of AFFSCI scores in patients in the main and control groups

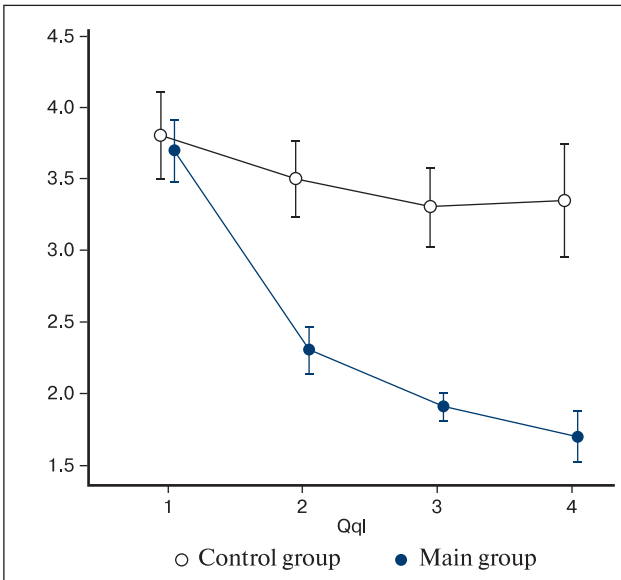

Fig. 3. Quality of life in patients in the main and control groups

There were no significant differences in the method of urine diversion between patients of two groups o (p=0.053). Patients receiving with fesoterodine showed a significant improvement in the ADFSCI after treatment (p<0.001); the results are shown in *fig. 2*. There was no dynamics in the control group (p=0.24) (*Table 1*). The quality of life according to the NBSS questionnaire also improved significantly in the main group (p<0.001) and did not change in the control group (*fig. 3*).

According to the ABPM and cystometry with simultaneous monitoring of blood pressure, in the main group there was a significant decrease in the number of episodes of AD, maximal daily SBP and diastolic blood pressure (DBP), maximum detrusor pressure, as well as SBP and DBP when cystometric capacity is reached. In addition, a significant increase in maximum bladder capacity and bladder compliance was found. These results demonstrate the positive effect of the drug. Comparative characteristics of the patients in the main and control groups are shown in *Table 2*.

Discussion. This study is the first one carried out in Russia, so it is not possible to compare our results with other domestic publications. A study of M. Walter et al., who followed-up 12 patients with SCI at or above the T6, has almost similar design [13]. The authors showed an increase in maximum detrusor capacity and quality of life in patients treated with fesoterodine. Our study is randomized and includes a large number of patients, as well as a variety of assessment tools.

S. Konstantinidis et al. showed that fesoterodine was an effective for NDO in patients with SCI or multiple sclerosis [15], which is consistent with the results of our study.

T. Yonguc et al. reported a significant reduction in the severity of overactive bladder symptoms in elderly patients with Parkinson's disease during long-term treatment with fesoterodine at a dose of 4 mg without effect on cognitive functions [16]. In another study, C. DuBeau et al. showed that fesoterodine (12-week treatment at a dose of 4 to 8 mg per day) not only significantly decreased a number of daily urge incontinence episodes and improved the quality of life in the elderly, but also did not adversely affect cognitive function compared with placebo [17]. In our study, the patients were younger and their cognitive functions were not assessed.

Considering the increased risk of cardiovascular disease in this cohort [18], our results are crucial, since a sudden increase in SBP can lead to life-threatening consequences, impairing the well-being and quality of life of people with SCI. Our study has limitations of a short follow-up (3 months), small sample size and the lack of data on the drug effect on cognitive function.

Conclusions. Our results suggest the efficiency of fesoterodine in a prevention of AD in patients with NDO

Table 1

Descriptive data of the study groups on ADFSCI parameter at the four time points

	Group	Mean value	Ст. отклонение	Минимум	Максимум	Медиана	Q1	Q3
ADFSCI	Control group	62.250	19.199	37.000	103.000	62.500	45.500	72.250
_1	Main group	62.212	27.513	8.000	116.000	62.000	45.000	82.000
ADFSCI	Control group	62.550	19.452	35.000	104.000	63.000	45.750	74.000
_2	Main group	38.727	18.163	7.000	76.000	36.000	24.000	51.000
ADFSCI	Control group	62.850	19.781	35.000	105.000	63.000	45.750	75.000
_3	Main group	34.909	15.489	7.000	68.000	34.000	23.000	43.000
ADFSCI	Control group	63.000	19.423	36.000	106.000	61.500	46.750	74.250
_4	Main group	30.818	12.358	7.000	57.000	32.000	20.000	39.000

Table 2

ABPM and cystometry parameters before and after treatment in fesoterodine groups

Parameter	Main group			Control group		
	до	после	*p*	до	после	*p*
Basic SBP, mm Hg	98.7±9.5	98.2±9.2	0.14	99.0±6.4	97.8±7.5	0.34
Basic DBP, mm Hg	62.7±4.8	62.1±4.5	0.67	62.6±3.3	62.4±7.1	0.88
Maximum daily SBP, mm Hg	162.0±31.1	129.2±18.3	<0.001	161.9±9.0	162.2±28.6	0.90
Maximum daily DBP, mm Hg	91.9±15.2	75.7±8.3	<0.001	92.2±14.7	89.1±21.5	0.27
Number of autonomic dysreflexia episodes according to ABPM	11.4±5.9	3.2±1.9	<0.001	11.6±5.0	10.5±5.1	0.11
Maximum bladder capacity, ml	232.7±64.5	296.2±60.5	<0.001	208.1±52.6	205.5±52.6	0.052
SBP at cystometric capacity, mm Hg	170.8±34.3	134.4±11.2	<0.001	140.6±9.1	143.3±10.8	0.056
DBP at cystometric capacity, mm Hg	102.5±21.3	80.1±9.3	<0.001	80.5±13.5	80.6±16.7	0.79
Maximum detrusor pressure, cm H_2O	38.3±15.0	17.2±5.6	<0.001	26.1±8.4	27.3±10.7	0.28
SBP at maximum detrusor pressure, mm Hg	160.7±27.7	130.3±13.2	<0.001	160.5±23.3	159.8±23.9	0.81
DBP at maximum detrusor pressure, mm Hg	93.4±15.8	77.1±9.2	<0.001	93.2±13.1	94.3±16.3	0.70
Bladder compliance	7.0±4.1	21.4±18.2	<0.001	9.1±4.8	9.4±6.5	0.7

secondary to SCI. The efficiency of the drug is confirmed by prevention of blood pressure rises, a decrease in detrusor overactivity, an increase in the cystometric capacity during pressure-study performed with blood pressure monitoring. A positive effect of fesoterodine on the quality of life of a selected cohort of patients was established, associated with a decrease in the severity and frequency of episodes of AD.

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HIFU THERAPY OF LOCALIZED PROSTATE CANCER USING IMAGE-GUIDED ROBOTIC HIFU «FOCAL ONE»

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Introduction. Prostate cancer (PCa) is the second most commonly diagnosed malignant tumor in men after lung cancer and is the fifth leading cause of death worldwide. In November 2019, the spectrum of alternative treatment for PCa was added by a novel minimally invasive method, namely high-intensity focused ultrasound (HIFU) using the latest Focal One machine (with the possibility of combining intraoperative ultrasound and preoperative MRI data).
Materials and methods. During the period from November 2019 to November 2021, HIFU using Focal One device (manufactured by EDAP, France) was performed in 75 patients with PCa. Total ablation was done in 45 cases, while 30 patients undergone to focal prostate ablation. The average age of the patients was 62.7 (51–80) years, the total PSA level was 9.3 (3.2–15.5) ng/ml and the prostate volume was 32.0 (11–35) cc. The maximum urinary rate was 13.3 (6.3–36) ml/s, IPSS score was 7 (3–25) points, IIEF-5 score was 18 (4–25). Clinical stage cT1cN0M0 was diagnosed in 60 patients, T1bN0M0 in 4 patients, T2N0M0 in 11 patients. In 21 cases, transurethral resection of the prostate was performed within 4–6 weeks prior to total ablation. Before surgery, all patients underwent magnetic resonance imaging (MRI) of the pelvis with intravenous contrast and PIRADS V2 assessment. MRI data were used intraoperatively for precision planning of the procedure.
Results. In all patients, the procedure was performed under endotracheal anesthesia in accordance with the technical recommendations of the manufacturer. Prior to surgery, a silicone urethral catheter of 16 or 18 Ch was placed. The average duration of the intervention was 101 (56–147) minutes. The postoperative period was uneventful in all cases.Patients received antibiotic therapy via parenteral route for 4 days, followed by oral administration for another 10 days, as well as alpha-blockers (at least 1 month after procedure). After removal of urethral catheter on the 4th day, all patients started to void. In 9 cases there was acute urinary retention in the evening and in 4 patients in the next morning, requiring temporary bladder catheterization. A year after the procedure, 53 patients were fully examined: the average total PSA level in patients who underwent total ablation (n=53) was 0.96±0.11 ng/ml, the IPSS score was 6.9±0,6 points (no difference compared to baseline). Follow-up biopsy revealed PCa in 6 patients; in other cases, prostate fibrosis was determined.
Conclusions. HIFU in patients with localized PCa using image-guided robotic HIFU (Focal One) is promising and feasible. This method has shown good oncological results with a short follow-up period. It is advisable to carry out further prospective analysis.

Key words: ultrasound ablation of the prostate, prostate cancer

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Introduction. More than 550,000 new cases of prostate cancer (PCa) are diagnosed annually in the world. Over the past decade, the number of actively detected cases of PCa in Russia has increased from 15.4% to 33.8% [1]. At the same time, 1-year mortality after a diagnosis for the same period decreased from 15 to 7.8%. This is an encouraging trend is due to many factors and proves the efficiency of early detection programs for PCa in Russia. Another confirmation is that in 2008 early-stage PCa was diagnosed in 44% of cases compared to 60.5% in 2020 [2, 3]. The progressive advancement in diagnostic methods and the introduction of prostate-specific antigen (PSA) screening into clinical practice in a number of countries allows to detect localized forms of PCa in 90% of patients [4, 5].

The introduction and selection of alternative treatment methods for patients with PCa with contraindications to radical prostatectomy remain controversial, as well-designed prospective studies describing standardized data are needed to perform before recommendations can be made on the use of total or focal ablative therapy in routine clinical practice (which is very unlikely in the near future) [6, 7].

Over the past 23 years, High-Intensity Focused Ultrasound (HIFU) has taken a unique path from its first procedure in 1999, performed by the professor of the Tokyo's University T. Ushida, to one of the main progressively developing minimally invasive methods for the treatment of localized PCa. In 2015, HIFU was included in the list of treatment methods for localized PCa in the United States, as recommended by the Food and Drug Administration (FDA) and the American Urological Association. At the same time, according to the European Association of Urology (EAU, 2023), due to the lack of solid comparative mid- and long-term oncological results, HIFU should be offered only as part of prospective studies [8].

HIFU is based on focused ultrasonic waves emitted by a transducer that cause tissue damage through mechanical, thermal and cavitation effects. The goal of HIFU is to raise the temperature of the tumor tissue above 75°C in order to destroy it by achieving coagulative necrosis.

Currently, there are three main types of devices for the treatment of patients with PCa, which are based on the emission of ultrasonic waves using a transrectal probe.

Apparatus "Sonablate" (Focal Surgery, USA) uses a 4 MHz piezoelectric probe for visualization, as well as for therapeutic effects. The distance from the lens to the focus is 3.0; 3.5 or 4.0 cm, energy power varies from 1680 to 2000 W/cm2. Currently, there are three such devices in Russia.

Apparatus «Ablatherm» (EDAP TMS SA, Vols de Velines, France) consists of two main stands, has a rectangular-shaped treatment probe with a concave surface in the form of a spoon of an electron matrix type with a focal length of 45 mm and therapeutic frequency of 3 MHz. The therapeutic sensor is combined with the diagnostic one (7.5 MHz). In 2021, 19 such devices were used in different clinics in the Russian Federation.

"Focal One" (EDAP TMS SA, Vols de Velines, France) is a new R-HIFU device of the latest generation, which consists of one mobile stand. The robot uses a single electron matrix probe with 3D robotic movements along three axes (in manual mode along 5 axes) with a longitudinal sequence length of 100 mm with a separate probe for visualizing real-time transrectal ultrasound (TRUS) 7.5 MHz and a separate multichannel probe for rHIFU therapy of 3MHz with dynamically changing focal volume (5–40 mm), thermal ablation rate 30 cm3/h, simultaneous use of 8 foci and penetration depth of 60 mm. In addition, there are "elastic-fusion" TRUS/MRI in the basic configuration, real-time guidance and visualization, robotic real-time auto-correction of the distance from the probe to the rectal wall with adjustment to its curvature, a system for cooling the rectal wall and controlling its temperature, and a sensor of the patient's external movements. Currently, in Russia, there are 3 robotic apparatus "Focal One", one of which is located in the clinic of Urology of the Moscow State Medical University on the basis of the GKB named after S. I. Spasokukotsky.

Its main advantages compared to the Ablatherm are:

- Novel eight-channel transducer significantly reduces ablation time, edema and cavitation effects, which results in improved quality of imaging.
- Miniature focal volume from 5 to 40 mm allows for extremely precise ablation.
- Fusion-guidance: a generation of a 3D MRI reconstruction of the prostate, followed by a real-time ultrasound fusion for even more precise visualization and delineation of the area of interest.
- Fully robotically-controlled temperature of the rectum, regardless of the position and activity of the Focal One system.
- Possibility of dynamic focusing.
- Small size of the device.

A localized PCa is the main indication for HIFU as definitive treatment, however, it is possible to use HIFU in locally advanced PCa as palliative treatment [9]. According to various authors, HIFU can be used to treat patients with low- and intermediate-risk PCa with contraindications for radical prostatectomy/radiation therapy or who refuse conventional treatment. In a number of studies devoted to the HIFU in patients with PCa, oncological and functional results at different follow-up periods are presented. They describe the good tolerability of HIFU with favorable profile of intra- and postoperative complications [10, 11].

Materials and methods. A total of 75 patients with verified PCa who underwent HIFU in the oncourological department of the City Clinical Hospital named after. S. I. Spasokukotsky DZM for the period from November 2019 to November 2021 were included in the study.

Inclusion criteria:

- localized PCa (stage ⩽T2);
- total PSA level <15 ng/ml;
- Prognostic group according to the International Society of Urological Pathology (ISUP)⩽3;
- absence of severe concomitant diseases in decompensation stage;
- informed consent.

As a primary treatment, HIFU was performed in 40 patients. In 5 cases, this method was used to treat tumor recurrence after external beam radiation therapy. In 30 patients focal HIFU was done as part of a clinical study. In total, our study included 70 (93%) patients with primary tumors who had not previously received treatment, and 5 (7%) with recurrent PCa, in which standard method was ineffective. The extent of the PCa was assessed based on the classification of the Union for International Cancer Control, and the TNM Classification of Malignant Tumors (UICC TNM) system (8th revision, 2017). The distribution of patients depending on the stage of the tumor is presented in *Table 1.* Patients with stage T1cN0M0 (80%) were predominated in the study.

Preoperatively, all patients underwent a standard clinical examination, including total serum PSA level, ultrasound of the urinary system, uroflowmetry with determination of the postvoid residual, contrast-enhanced pelvic MRI (or a re-evaluation of the MRI results obtained from another clinic), and perineal saturation biopsy of the prostate to determine the exact localization of the tumor foci if focal treatment was planned. In patients who had prostate biopsy in another clinic, the review of biopsy slides was done to verify the ISUP prognostic group [12, 13].

The treatment was carried out under general anesthesia using the Focal One robotic complex (the use of nitrous oxide was strongly discouraged, since this gas affects the quality of ultrasound images during treatment by increasing the cavitation effect and, as a result, increasing the duration of the procedure). This device was equipped

with a single electron array probe with 3D robotic movements with a separate transducer for real-time 7.5 MHz TRUS imaging and a separate multichannel 3 MHz transducer for rHIFU therapy with dynamically variable focal volume (5–40 mm). The procedure was done under the strict control of security systems: firstly, during the ablation phase, the software automatically controls the distance from the treatment probe to the rectal wall, and the cooling system maintains the temperature of the rectal mucosa at 14°C; secondly, the position of the "focal" point inside the prostate was controlled by the surgeon in real time; thirdly, the device had a sensor of the patient's external movements, which, at the slightest movement, would instantly stop the system. Actually, this algorithm allowed to call this system robotic.

The ultrasound transducer was advanced transrectally with the patient lying on the right side (*fig. 1*). Treatment planning was done with diagnostic ultrasound followed by an overlaying of MRI images and preoperative biopsy data when fusion 3D modeling was performed (*fig. 2*).

The urologist performed contouring of the prostate to plan the area of ultrasound ablation. In addition, it was mandatory to set a border of 4–6 mm from the sphincter to prevent its injury (*fig. 3*).

The larger the prostate, the longer the HIFU was performed, and therefore every patient scheduled for total HIFU with a prostate volume >35 cc and/or bladder outlet obstruction/lower urinary tract symptoms (LUTS) (total IPSS score >19) was undergone to transurethral resection of the prostate (TURP) at the first stage in order to reduce the anteroposterior size of the prostate and ensure the technical feasibility of total ablation.

Fig. 1. Patient position during the procedure

The average length of stay of patients who underwent HIFU was 4.5 days, depending on the extent of ablation. After a focal ablation the urethral catheter was removed on the 3rd day, and after total ablation on the 4th day. From the first postoperative day each patient was prescribed a selective α1-adrenergic receptor blocker for 30 days in the absence of contraindications to reduce the tone of the smooth muscles of the prostate, bladder neck and prostatic part of the urethra.

During hospital stay, each patient received infusion, anti-inflammatory and antibacterial therapy, subsequently extended on an outpatient basis up to 30 days to minimize postoperative inflammation.

Table 1

Distribution of patients by stages of the disease according to the UICC TNM system

Stage	*n*	%
T1bN0M0	4	4,5
T1cN0M0	60	80
T2N0M0	11	15,5
Total	75	100

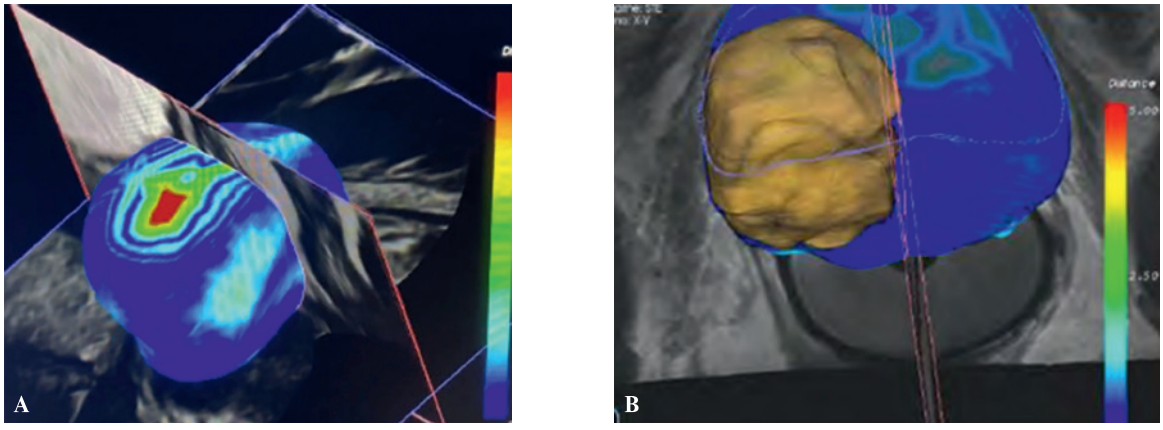


Fig. 2. 3D model of the prostate.
A - matching the boundaries (fusion) of the prostate according to TRUS and MRI prior to procedure. 3D mode.
B - Visualization of the suspicious area in the prostate. 3D mode.

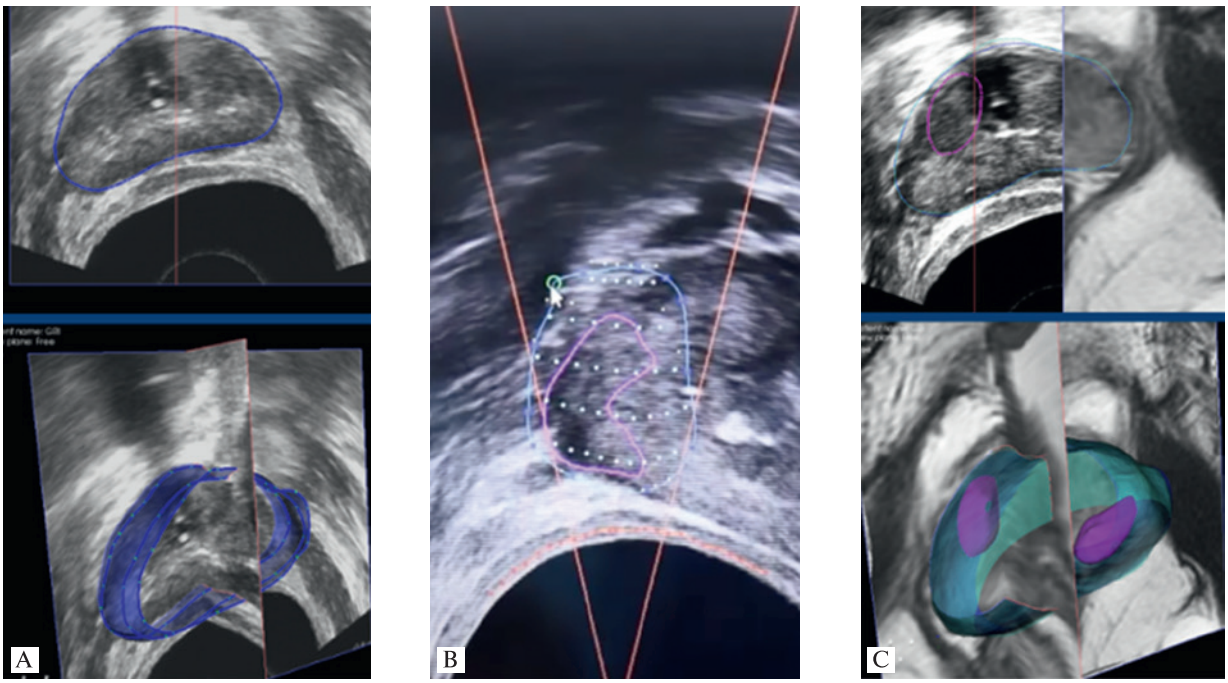


Fig. 3. Stages of the planning of the areas of ultrasound ablation
A – outlining the boundaries ("outlining") of the prostate; B - outlining the boundaries of the target zone for ablation; C – comparison of TRUS and MRI data in real time (fusion).

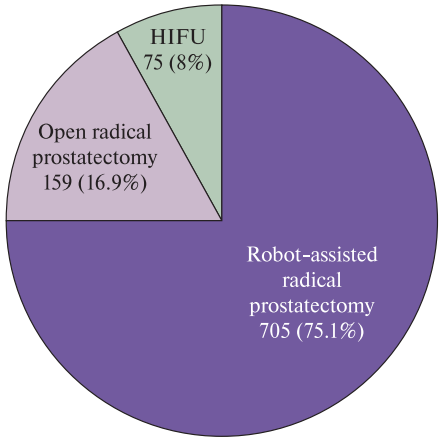


Fig. 4. Types of surgical procedures in patients with prostate cancer performed in the urologic clinic of the Moscow State Medical University on the basis of the City Clinical Hospital named after S.I. Spasokukotsky DZM from November 2019 to November 2021

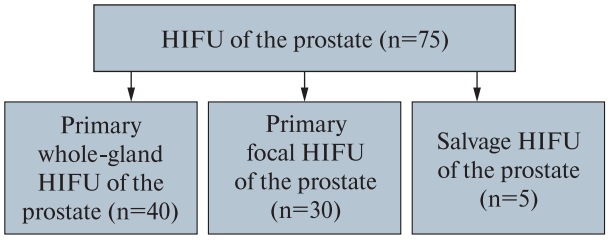


Fig. 5. Распределение пациентов в зависимости от вида HIFU

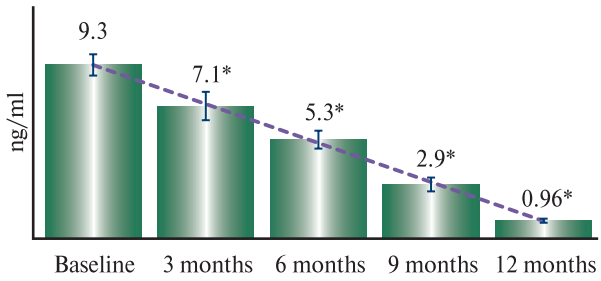
To assess the result of the HIFU in the absence of contraindications, a year later, patients underwent contrast-enhanced pelvic MRI.

The main criteria for the efficiency of treatment were the lowest value (nadir) of PSA and negative follow-up biopsy a year after procedure.

Statistical data analysis was performed using Statistica 12.0 software (StatSoft, USA). The normality of the distribution of values in the sample was assessed using the Shapiro–Wilk test. Statistical significance of differences in quantitative parameters between groups was carried out using the Mann-Whitney test, while for proportions Pearson's Chi-squared test with Yates' correction for continuity was performed. In dynamics, the average values were compared to the baseline using the Wilcoxon test. To identify statistical differences, the critical confidence level p was taken as 0.05.

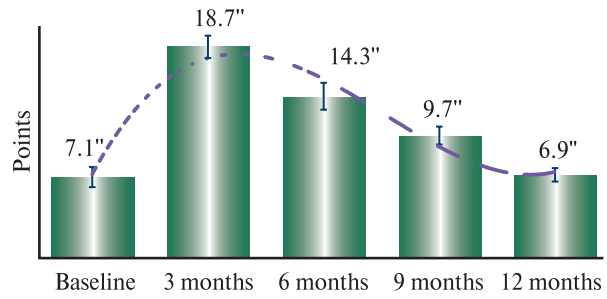
Results. From November 2019 to November 2021 in the oncourological department of the City Clinical Hospital named after. S. I. Spasokukotsky DZM a total of 939 patients with PCa were treated (from 04/20/2020 to 07/16/2020, the surgical activity of the clinic was suspended due to the epidemiological situation caused by the COVID-19 pandemic). The age of patients was 62.2±2.4 (min=51, max=80). 705 (75.1%) patients underwent robot-assisted radical prostatectomy, 159 (16.9%) retropubic radical prostatectomy and in 75 (8%) cases HIFU was done (*fig. 4*). 28% of patients (*n*=21) underwent TURP at the first stage. In 40 (53.3%) patients, total HIFU was primary treatment method, while in 5 (6.7%) a salvage total ablation in case of a recurrence after external beam radiation therapy or brachytherapy was done, and in 30 (40%) of cases, focal therapy was performed as part of a separate clinical protocol (*fig.5*).

The main characteristics of the patients are shown in *table 2.*



* – significant differences compared to the preoperative level at p<0.05.

Fig. 6. Dynamics of the PSA level in patients with localized prostate cancer after HIFU (n=53)



" – nonsignificant differences compared to the preoperative level at p<0.05.

Fig. 7. Dynamics of IPSS in patients with localized prostate cancer after HIFU (n=53)

Significant differences between subgroups were found for the distribution of patients depending on the clinical stage, ISUP prognostic group, prostate volume and erectile function. There were no differences in age, Qmax and IPSS score. Serum PSA level ranged from 3.2 to 15.5 ng/ml (mean 9.3). The average prostate volume was 32 (11–50) cc. This subgroup of patients did not have severe LUTS (mean IPSS score 7 [3-25]). Most men were interested in maintaining erectile function (IIEF-5 score 5 points [4–25]).

A year after HIFU, 53 (70.6%) patients were fully examined. The dynamics of the total PSA level and IPSS score during the first 12 months was analyzed (*fig. 6* and *7*). In most cases, there was a steady trend towards a postoperative decrease in the total PSA level from 1 to 12 months. At the end of the first year, mean PSA value was 0.96±0.11 ng/ml. The mean postvoid residual was 83 (0–150) ml.

After 3 months after HIFU, the severity of LUTS increased: the IPSS score worsened from 7.1±0.9 to 18.7±1.0 points (p=0.017), which corresponded to moderate severity. After 6 and 9 months. there was a decrease in the IPSS score with the normalization of urination after 12 months. Total IPSS score at the end of the first year was 6.9±0.6 points, which did not differ compared to baseline (p>0.05).

After 1-year follow-up, there were no serious complications according to the Clavien–Dindo

Table 2

Baseline characteristics

Factor	Statistical value	Total in the group (n=75)	Primary total ablation (n=40)	Salvage total ablation (n=5)	Focal ablation (n=30)	p
Age, years	M±m	62.2±2.4	61.7	64.5	63.6	>0.05 P vs S. F vs P/S
	Me [25-75]	61 [57-69]	63 [55-67]	65 [57-70]	64 [58-68]	
	Min-Max	51-80	51-76	53-80	56-74	
Clinical stage:						=0.043
T1bN0M0	abs. (%)	4 (5.3)	1 (2.5)	–	3 (10.0)	P vs S.
T1cN0M0		60 (80.0)	33 (82.5)	–	27 (90.0)	<0.001
T2N0M0		11 (14.7)	6 (15.0)	5 (100.0)	–	F vs P/S
Prognostic group:						=0.48
1	abs. (%)	50 (66.7)	19 (47.5)	1 (20.0)	30 (100)	P vs S
2		14 (18.7)	12 (30.0)	2 (40.0)	–	<0.001
3		11 (14.6)	9 (22.5)	2 (40.0)	–	F vs P/S
Prostate volume, cc	M±m	31.6±1.9	30.2±2.0	21.5±1.5	32.8±1.8	=0.016 S vs P/F =0.89 P vs F
	Me [25-75]	32 [28-34]	31 [27-33]	22 [17-25]	32 [28-34]	
	Min-Max	11-35	13-34	11-28	12-35	
Q max, ml/sec	M±m	12.9±0.8	11.7±0.7	14.2±0.9	17.3±0.8	>0.05 P vs S. F vs P/S
	Me [25-75]	13.3 [11.2-16.9]	12.4 [10.9-16.3]	14.9 [12.4-17.5]	16.8 [13.7-19.4]	
	Min-Max	6.3-36	6.3-28.5	8.9-36	6.8-34.3	
IIEF, points	M±m	18.1±1.0	17.4±0.9	5.5±0.3	22.2±1.1	<0.001 S vs P/F =0.21 P vs F
	Me [25-75]	18 [15-22]	17 [14-19]	6 [5-9]	21 [18-23]	
	Min-Max	4-25	11-20	4-12	16-25	
IPSS, points	M±m	7.1±0.9	6.9±0.7	8.5±0.9	6.7±0.8	>0.05 P vs S. F vs P/S
	Me [25-75]	7 [5-10]	7 [4-9]	9 [6-11]	6 [5-10]	
	Min-Max	3-25	6-24	3-25	4-19	

Note. Q max, maximal flow rate; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score, M, mean; m, mean error; Me, median, [25-75], interquartile range; Min-Max, range; P, primary; S, salvage; F, focal ablation; vs, in comparison.

classification (the maximum grade was I–II). 49 (92.4%) patients had no urinary continence, while in 3 (5.6%) patients, urge urinary incontinence developed with 3-7 episodes a week (they used no more than 1 pad per day).

Of all 53 patients, there were 5 (9.4%) cases of acute urinary retention (after removal of the urethral catheter). All of them had normal voiding after re-insertion and subsequent removal of the urethral catheter. In 1 (1.9%) patient who underwent simple prostatectomy before HIFU, total urinary incontinence developed.

Among the fully examined patients, 35 men were interested in maintaining erectile function. 17 (48.5%) patients were undergone to total ablation of the prostate, while 18 (51.5%) patients had focal ablation. After 3 months, there was a deterioration in erectile function in both groups, however, when followed up for a year, 89% of patients after focal ablation had enough erection for penetration. In men who underwent total ablation of the prostate, enough erection was preserved in 71% of cases. The average percentage of preservation of erectile function after HIFU was 80%. The mean IIEF-5 score was 18 points.

In 4 (12%) of 32 patients who underwent total ablation, a relapse was detected after 12 months. A year after focal HIFU, follow-up biopsy was performed in 21 (70%) of 30 patients. Among them, fibrous and atrophic tissue was detected in 19 (90.5%) of cases, PCa in 2 (9.5%). Among 2 patients with recurrence of PCa, active follow-up was recommended for 1 patient, while another man was referred for external beam radiation therapy.

Conclusion. HIFU of the prostate has been used in clinical practice for over 20 years. Technical innovations and the introduction of fusion technologies allow improving treatment outcomes. The initial experience of the urological clinic of the Moscow State Medical University of Dentistry demonstrated good short-term oncological results. Acceptable tolerability of treatment, minimal number of side effects and complications, rapid recovery and preservation of quality of life were found. It is highly recommended to carry out further prospective analysis. In our opinion, the method of HIFU of the prostate using a robotic complex "Focal One" is promising and appropriate in the treatment of patients with PCa. However, further studies are required in order to determine its place in the hierarchy of organ-preserving and functionally sparing treatment methods of PCa.

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ANDROGENIC STATUS OF MEN WITH SEVERE COVID-19: THE ROLE OF TESTOSTERONE AND DIHYDROTESTOSTERONE [WITHIN THE PROGRAM FOUNDER (FEATURES OF A NEW CORONAVIRUS INFECTION COURSE AND OPTIONS THERAPY DEPENDING ON THE ANDROGENIC STATUS)]

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Purpose. The aim of this study was to assess the men's androgen status influence on the severity and outcomes (transfer of patients to the ICU or death) of COVID-19 required hospital hospitalization.
Materials and methods. The study included 151 hospitalized men with a confirmed diagnosis of COVID-19. To measure the severity of disease have been used Symptomatic Hospital and Outpatient Clinical Scale for COVID-19 (SHOCS-COVID). It includes the severity of the clinical condition (hyperthermia, shortness of breath, oxygen saturation, need for ventilation), the degree of inflammation (CRP), markers of thrombosis (D-dimer), the degree of lung damage according to CT. The patients underwent a study of full blood count, some biochemical parameters, lung CT, and a study of testosterone (T) and dihydrotestosterone (DHT) levels.
Results. T deficiency was observed in 46.4% of patients (70/151 men). At the same time, DHT deficiency was observed only in 14.4% of patients (18/125 men). In patients with a T level below the median, there was a significant increase in inflammatory factors (CRP, lymphocytes/CRP index), markers of thrombosis (D-dimer and fibrinogen), extensive lung damage at admission according to CT 25.75% vs. 11.95% ($p<0.001$), the elevated number of points for SHOCKS-COVID 7 (IQR 5-10) versus 5 (IQR 3-7) ($p<0.001$) and the longer duration of hospital treatment (3 days difference, $p<0.001$) in comparison with a group of patients with a T level above the median. At the same time, the T level had no correlation with age. The level of DHT had a weak inverse correlation with the age of patients, but not with the main markers of the severity of COVID-19, including the number of SHOCK-COVID scores.
During multivariate regression analysis, it was shown that SHOCKS-COVID is the most significant predictor of admission to the ICU while no association of T and DHT levels with outcomes in COVID-19 was found. However, it was found that the concentration of T, even adjusted for age, has a significant inverse association with the severity of the course of the disease and the number of SHOCK-COVID scores ($p=0.041$). An analysis of the evaluation of directed acyclic graphs suggests the main role of COVID-19 severity in reducing androgenic function and T concentration, at which its anti-inflammatory effects are lost. There were no correlations between the concentration of DHT and the number of SHOCK-COVID scores and the COVID-19 prognosis.
Conclusion. SHOCK-COVID is the most sensitive predictor of the COVID-19 outcome in hospitalized men, including adjusting to age. T and DHT do not directly affect the outcomes of the disease. The greater severity of the infection and an increase in SHOCK-COVID scores are associated with a decrease in the concentration of T, and a weakening of its anti-inflammatory and anti-cytokine effects, which indirectly worsens the prognosis of male patients with a new coronavirus infection undergoing hospital treatment. There are no such relationships for DHT.

K e y w o r d s: testosterone, dihydrotestosterone, COVID-19

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Introduction. From the very beginning of the pandemic of a new coronavirus infection, gender differences in the risk of development and severity of the infection were intriguing [1]. It is now generally accepted that one of the risk factors for a more severe course of COVID-19 is male gender [2].

An important reason for greater risk of both the development and a more severe clinical course of COVID-19 in men may be the accelerated penetration of the SARS-CoV-2 virus into the epithelial cells of the lung alveoli, which is accompanied by a rapid viremia [1]. The two main receptors required for virus entry into cells are angiotensin-converting enzyme type 2 (ACE2) "anchored" on the cell membrane and type 2 transmembrane serine protease (TMPRSS2) [3]. Even before pandemic of COVID-19, it was known that the androgen receptor is the main regulator of TMPRSS2 transcription, since it increases it upon activation by androgens [3]. In vitro studies have shown that the expression of both ACE2 and TMPRSS2 is under the influence of the active metabolite of testosterone (T), dihydrotestosterone (DHT) [4]. Therefore, in the early stages of studying a new coronavirus infection, androgenic status of men was suggested to be a reason of a more severe course of COVID-19 [5, 6]. A retrospective analysis of non-randomized studies, including those carried out by our group, showed that androgen deprivation therapy, which results in a decrease in DHT concentration and an improvement of the course of benign prostatic hyperplasia and prostate cancer, is associated with a lower risk of developing a new coronavirus infection [7, 8]. This issue was analyzed in the study BISKVIT, performed at the clinic of the Medical Scientific and Educational Center of Moscow State University in 2020 [9]. With early initiation of COVID-19 treatment with a combination of bromhexine, blocking TMPRSS2 activity [10], and spironolactone, which has a nonspecific antiandrogenic effect, reducing a level of T and DHT, and the activity of both ACE-2 and TMPRSS2, more rapid normalization of the clinical condition was seen [9].

However, in patients with new coronavirus infection, especially with lung damage, who require an admission to the clinic, hormonal patterns change. In this case, a decrease in androgenic status, determined mainly by T level, is associated with an unfavorable course of COVID-19 [11, 12]. Our group demonstrated that low T levels in men hospitalized with moderate to severe COVID-19 were associated with more pronounced infiltrative changes in the lungs, high levels of C-reactive protein (CRP), D-dimer, and more prolonged and intensive treatment [13]. There are paucity data on the relationship of DHT with the severity and prognosis of a new coronavirus infection. One study showed lower DHT levels in ICU patients with COVID-19 than in healthy volunteers, but authors were mainly focused on T [14]. We attempted to fill this gap by simultaneously analyzing the levels of both T and DHT in men hospitalized with COVID-19 at the clinic of the Medical Scientific and Educational Center of Moscow State University.

Aim. To evaluate the impact of androgenic status (T and DHT) in men on the severity of the course and outcomes of moderate-severe and severe COVID-19.

Materials and methods. A single-center prospective study included 151 men admitted at the Medical Scientific and Educational Center of Moscow State University named after M. V. Lomonosov from April 21, 2020 to June 13, 2020 with confirmed COVID-19 (according to a positive PCR test from the nasopharynx for SARS-Cov-2 RNA), in which the serum T and DHT levels were determined.

To objectify the severity of the clinical condition and evaluate the efficiency of therapy, two scales were used: the National Early Warning Score (NEWS) [15], modernized for patients with COVID-19 [10], and our original scale for assessing the clinical condition of patients with new coronavirus infection (SHOKS-COVID) [16].

Biochemical analyzes were performed at admission and after 12 (+/-2) days or at discharge, if it occurred earlier. Computed tomography of the lungs and chest organs was done on a 32-slice Somatom Scope CT scanner (Siemens Germany). For the quantitative analysis of infiltrative changes in the lungs with COVID-19, the Multivox software (developed by Gammamed, Moscow) and Botkin.AI (developed by company "Intelodzhik", Moscow) were used. The research methodology is described in detail in our previous articles [9, 17].

The determination of serum T level was carried out using an automatic analyzer Roche Cobas 6000 by immunochemiluminescence assay with the Elecsys Testosterone II test system. Reference values, as well as all other information on the Elecsys Testosterone II test system for determining serum T level, was obtained from the manufacturer's instructions, which is attached to the test system. The lower limit of serum T in accordance with the instructions was 2.49 ng/ml in those under 50 years of age (range – 2.49–8.36 ng/ml) and 1.93 ng/ml in men over 50 years of age (range – 1.93-7.40 ng / ml).

Serum DHT level was determined using the Elecsys Testosterone II Immunoassay (analyzer Roche Cobas 6000). Reference values, as well as all other information on the test system were obtained from the manufacturer's instructions that are attached to the test system. The lower and upper limits of the serum DHT level in men, in accordance with the instructions for the test system, were 175 and 1204 pg/ml, respectively.

Statistical analysis. The normality of distribution was assessed using the Shapiro–Wilk and the Kolmogorov–Smirnov tests. The quantitative data are presented as median and interquartile range (median and 25%; 75%) in case of non-parametric distribution and as mean and standard deviation (SD) in case of normal distribution. Comparison of quantitative characteristics between groups was carried out using the Mann-Whitney test with non-parametric data distribution and using Student's T-test with normal distribution. Qualitative data are presented as absolute and relative values. The significance of differences in qualitative characteristics was assessed based on the chi-square ($\chi 2$) test, as well as the Fisher's exact test. The Spearman's rank correlation coefficient was used to evaluate the correlation between parameters. In addition, logistic regression (for a binary dependent variables) and linear regression (for a continuous dependent variable) were used. Differences were considered significant at $p<0.05$.

Results. In the whole sample of men with COVID-19 (n=151), the median T was 2.15 ng/ml (IQR 1.21-3.42). T deficiency was observed in 70 (46.4%) of cases. The median DHT (measured in 125 patients) was 374.00 pg/mL (IQR 242.70–557.90). At the same time, DHT deficiency was observed only in 18 (14.4%) patients, while

in 85.6% of cases, DHT remained within normal values. In *Table 1* a comparison of characteristics between groups of patients divided according to T level above (n=75) and below (n=76) median, as well as in accordance with DHT level above (n=63) and below (n= 62) median are presented.

In patients with low T levels, all markers of systemic inflammation (CRP, leukocytes, neutrophils, neutrophil to lymphocyte ratio, lymphocyte-to-C-Reactive protein ratio) were significantly increased compared to patients with normal T levels. During the follow-up a difference for most markers persisted, but became less pronounced. Similarly, the risk of thrombosis, as measured by D-dimer and fibrinogen, was significantly higher in patients with low T levels. In addition, in those with low T levels, the lung injury on CT was more than twice as large (25.75 vs. 11.95%), compared to patients with normal T level. The severity of clinical condition according to NEWS-2 (<0.002) and the overall severity based on SHOKS-COVID (p<0.001) were significantly higher in patients with T levels below the median.

In this group, corticosteroids were prescribed significantly more often, and patients with low T level were significantly more likely to be admitted to the ICU, required mechanical ventilation. In addition, improvement of their condition required three more days (<0.002).

Men with COVID-19 with DHT levels below the median were significantly older, with a lower body mass index, than those with DHT levels above the median. With regard to inflammatory markers and markers of thrombus formation, the severity of the clinical condition (NEWS-

Table 1

A comparison of characteristics of patients with T below vs. above the median; DHT below vs. above the median

	T is below the median (n=76)	T is above the median (n=75)	p	DHT below median (n=62)	DHT is above the median (n=63)	p
Clinical characteristics						
Age, years, median (IQR)	58.00 (47.00–67.00)	58.00 (39.00–70.00)	0.598	64.00 (52.00–73.00)	51.00 (39.00–59.00)	**<0.001**
BMI. kg/m^2. median (IQR)	29.37 (25.95–33.03)	28.69 (25.40–32.32)	0.233	27.68 (25.62–30.68)	30.19 (25.83–33.26)	**0.046**
Testosterone, ng/ml, median (IQR)	1.22 (0.78–1.59)	3.42 (2.64–4.75)	**<0.001**	1.44 (0.93–2.98)	2.05 (1.38–3.30)	0.127
DHT, пг/мл, median (IQR)	369.20 (230.95–575.10)	379.10 (242.70–557.90)	0.620	242.25 (151.40–323.10)	557.90 (465.20–798.20)	**<0.001**
HTN, % (n)*	52.63 (40)	52.7 (39)	0.993	59.02 (36)	47.62 (30)	0.204
CAD, % (n)**	14.47 (11)	13.51 (10)	0.865	18.03 (11)	7.94 (5)	0.159
DM, % (n)**	19.74 (15)	10.81 (8)	0.129	16.39 (10)	12.70 (8)	0.742
Oncologic diseases, % (n)***	5.26 (4)	4.05 (3)	1.000	8.20 (5)	3.17 (2)	0.269
Time point 1 – baseline charateristics						
Lung injury on CT, %, median (IQR)	25.75 (7.90–49.70)	11.95 (4.30–29.45)	**<0.001**	20.20 (5.80–45.80)	17.30 (5.90–36.80)	0.593
CRP, mg/l, median (IQR)	88.12 (45.54–147.45)	40.22 (10.80–86.96)	**<0.001**	48.78 (17.35–98.27)	67.67 (23.01–130.01)	0.059
D-dimer, mkg/ml, median (IQR)	0.76 (0.40–1.14)	0.42 (0.28–0.96)	**0.023**	0.76 (0.37–1.37)	0.54 (0.31–1.07)	0.316
Fibrinogen, g/l, mean±SD	6.16±1.72	5.35±1.61	**0.005**	5.46±1.86	5.99±1.34	0.078
Leukocytes, 10^9/l, median (IQR)	6.18 (4.87–7.58)	5.52 (3.77–6.48)	**0.004**	5.37 (4.26–6.89)	6.12 (4.06–7.37)	0.210
Neutrophils (H), 10^9/l, median (IQR)	4.48 (2.97–6.21)	3.55 (2.21–4.62)	**0.002**	3.65 (2.72–5.33)	4.15 (2.60–5.57)	0.444
Lymphocytes (Л), 10^9/l, median (IQR)	1.19 (0.82–1.61)	1.14 (0.88–1.65)	0.457	1.15 (0.72–1.62)	1.20 (0.91–1.65)	0.213
Neu/Leu ratio, median (IQR)	3.75 (2.30–6.27)	2.97 (1.86–4.47)	**0.014**	3.43 (2.13–5.61)	3.16 (2.10–4.96)	0.731
Leu/CRP ratio, median (IQR)	15 (6–32)	28 (13–100)	**<0.001**	23 (11–72)	17 (9–46)	0.241
NEWS-2 score	3.00 [1.00;5.00]	4.00 [2.00;7.50]	**0.004**	3.00 [2.00;6.00]	4.00 [2.00;7.00]	0.275
SHOKS-COVID score, median (IQR)	7.00 (5.00–10.00)	5.00 (3.00–7.00)	**<0.001**	7.00 (4.00–8.50)	5.00 (4.00–9.00)	0.805
Time point 2 – charateristics after 12+/-2 days or at discharge, if it was earlier						
CRP, mg/l, median (IQR)	9.74 (4.19–20.77)	5.37 (3.22–17.94)	0.058	7.78 (2.92–20.84)	7.57 (3.59–16.87)	0.965
D-dimer, mkg/ml, median (IQR)	0.73 (0.50–1.22)	0.49 (0.25–1.27)	**0.041**	0.66 (0.30–1.63)	0.61 (0.31–1.02)	0.254
Fibrinogen, g/l, mean±SD	5.59±1.65	4.87±1.60	0.05	5.24±1.56	5.48±1.76	0.566
WBC, 10^9/l, median (IQR)	6.24 (5.11–8.44)	5.72 (4.25–6.62)	**0.012**	6.25 (4.92–8.44)	5.92 (4.58–6.73)	0.249
Neutrophils (Neu), 10^9/l, median (IQR)	3.50 (2.45–5.73)	2.89 (2.10–4.04)	**0.019**	3.29 (2.13–5.19)	3.00 (2.27–3.28)	0.357
Lymphocytes (Leu), 10^9/l, median (IQR)	1.77 (1.12–2.13)	1.66 (1.30–2.34)	0.283	1.65 (1.12–2.19)	1.94 (1.42–2.27)	0.061
Neu/Leu ratio, median (IQR)	1.81 (1.36–4.05)	1.62 (1.10–2.07)	**0.021**	1.86 (1.36–3.76)	1.62 (1.24–1.93)	0.074
Leu/CRP ratio, median (IQR)	170 (70–450)	340 (90–600)	**0.034**	180 (39–641)	262 (96–528)	0.405
Outcomes						
Use of steroids, % (n)*	27.03 (20)	8.33 (6)	**0.003**	27.87 (17)	14.75 (9)	0.077
Length of stay, days, median (IQR)	13.00 (10.00–17.50)	10.00 (7.00–14.00)	**0.002**	12.00 (10.00–17.00)	11.00 (7.00–15.00)	0.071
PE/thrombosis, % (n)***	5.26 (4)	4.17 (3)	1.000	8.20 (5)	3.28 (2)	0.439
Admission to ICU, % (n)*	23.68 (18)	9.33 (7)	**0.018**	20.97 (13)	12.70 (8)	0.216
Length of stay in ICU, days, median (IQR)	12.50 (4.00–21.00)	12.00 (3.00–16.00)	0.717	16.00 (12.00–28.00)	5.00 (2.50–13.00)	**0.036**
Use of mechanical ventilation, % (n)**	15.79 (12)	4.00 (3)	**0.032**	17.74 (11)	4.76 (3)	**0.044**
Duration of mechanical ventilation, days, median (IQR)	13.00 (9.00–17.00)	8.00 (0.00–33.00)	0.554	13.00 (9.00–33.00)	13.00 (9.00–37.00)	0.876
Death, % (n)***	6.58 (5)	2.67 (2)	0.442	6.45 (4)	3.17 (2)	0.440

* – χ^2. ** – χ^2 with Yates correction. ** Fisher's criterion

2) and the overall severity of COVID-19 (SHOKS-COVID), there were no significant differences between patients depending on DHT level, both at admission and over the time. Patients with DHT level below the median were admitted to the ICU with the same frequency as those with normal DHT, but length of stay in the ICU was significantly longer and they significantly more often required the mechanical ventilation. The frequency of prescription of corticosteroids and the length of stay in the hospital did not differ significantly regardless on DHT level.

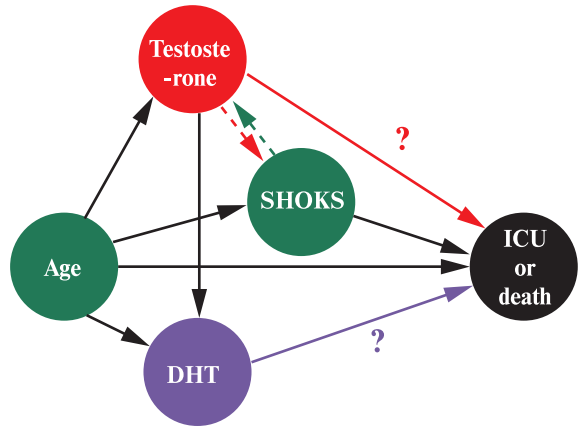
The analysis of correlations between T and DHT levels, on the one hand, and clinical characteristics and manifestations of a new coronavirus infection, on the other hand, are presented in *Table 2*. It has been shown that low T level is associated with more pronounced inflammatory processes. For DHT, there was virtually no correlation with COVID-19 manifestations. The exception is a weak positive correlation with CRP levels, which can be interpreted with caution as greater inflammation with higher DHT levels. Based on the obtained results and published data, a directed acyclic graph for patients' admission to the ICU or death (see figure) was created.

Black lines show reliable relationships, and lines with question marks show the associations that were the subject of this study. The distinct feature was that the original SHOKS-COVID scale was used as an integral indicator of the severity of manifestations of COVID-19.

Multivariate logistic regression models describing the likelihood of a more severe course of COVID-19, expressed in the need to transfer patients to the ICU or death, taking into account T and DHT level, are presented in *Table 3*.

The first model (sensitivity 57.1%) included, in addition to the age and severity of COVID-19 according to SHOKS-COVID, T level. As can be seen, neither T level nor age determined the risk of unfavorable COVID-19 course. The main significant factor for the transfer of patients to the ICU or death was SHOKS-COVID score: with an increase in each additional point, the chances of an unfavorable outcome more than doubled (OR=2.016; 95% CI=1.480–2.747; $p<0.001$).

Taking into account the correlation between T and the severity of COVID-19 according to SHOKS-COVID, it is possible to assume two variants of the associations presented in *fig. 1* as colored dotted lines. If we assume the primacy of the severity of COVID-19 course and it is accompanied by a decrease in T level, then the dependence is represented by a green dotted line. In this case, our first model of multifactor relationships will be



Note: this figure consists of two directed acyclic graphs with the only difference, namely the direction of the arrow from T to SHOKS or from SHOKS to T. please, refer to the text for more details.

Figure. Directed acyclic graph for admission to the ICU or death of male patients with moderate or severe COVID-19

Table 2

Correlation analysis results for testosterone и DHT

	r (T)	*p*	*r* (DHT)	*p*
Clinical data				
Age, years	-0.113	0.168	**-0.391**	**<0.001**
BMI, kg/m^2	**-0.184**	**0.027**	0.168	0.068
Time point 1 – baseline data				
Lung injury on CT, %, median (IQR)	**-0.238**	**0.008**	-0.019	0.833
CRP, mg/l	**-0.310**	**<0.001**	**0.215**	**0.016**
D-dimer, mkg/ml	-0.154	0.060	-0.091	0.316
Fibrinogen, g/l	-0.051	0.707	0.223	0.132
Leukocytes, 10^9/l	**-0.178**	**0.028**	0.105	0.242
Neutrophils, 10^9/l	**-0.194**	**0.017**	0.088	0.328
Lymphocytes, 10^9/l	0.025	0.763	0.056	0.534
Neu/Leu ratio, median (IQR)	-0.157	0.080	0.025	0.779
Leu/CRP ratio, median (IQR)	**0.218**	**0.015**	-0.169	0.064
NEWS-2 score, median (IQR)	**-0.264**	**0.003**	-0.119	0.187
SHOKS-COVID score, median (IQR)	**-0.344**	**<0.001**	0.050	0.584
Outcomes				
Length of stay, days	**-0.321**	**<0.001**	-0.159	0.077
Length of stay in ICU, days	-0.275	0.183	-0.383	0.087
Duration of mechanical ventilation, days	-0.182	0.471	0.182	0.534

Table 3

Multivariate logistic regression models for the endpoint "ICU or death" taking into account the levels of T and DHT

	OR (95% CI)	*p*
ОРИТ		
Model 1, sensitivity 57,1%, p<0.001		
SHOKS-COVID	**2.016 (1.480–2.747)**	**<0.001**
Age	1.054 (0.998–1.114)	0.060
T	0.973 (0.674-1.405)	0.885
Model 2. sensitivity 4%. p=0.003		
Age	**1.040 (1.008–1.076)**	**0.017**
T	**0.720 (0.501–0.959)**	**0.045**
Model 3. sensitivity 61.9%. p<0.001		
SHOKS-COVID	**2.195 (1.551–3.105)**	**<0.001**
DHT	0.998 (0.995–1.000)	0.080
Age	1.039 (0.982–1.098)	0.181
Model 4. sensitivity 61.9%. p<0.001		
SHOKS-COVID	**2.212 (1.550–3.156)**	**<0.001**
Age	1.039 (0.983–1.100)	0.177
T	1.045 (0.722–1.511)	0.817
ДГТ	0,998 (0,995–1,000)	0,078

correct. But the opposite cannot be ruled out, that a low T level determines the severity of COVID-19 (red dotted arrow in Fig. 1) and SHOKS-COVID is a mediator of the influence of T on the risk of admission to the ICU or death of men. To test this assumption, a second model was created that excluded SHOKS-COVID from the analyzed factors. In this case, both age and, as we tested, low T level were associated with risks of adverse outcomes. However, the sensitivity of the model without SHOKS was very low (only 4%), therefore we conclude that even if low T levels affect SHOKS-COVID score, this is not the only and not the main factor of severity.

The third model is similar to the first one with the only difference that instead of T, the possible influence of DHT along with age and SHOKS-COVID on the risk of transfer to the ICU or death was studied. With a sensitivity of 61.9%, neither DHT nor age were significant factors, and only an increase in disease severity for each additional SHOKS-COVID score doubled the chance of ICU admission or death in men with COVID-19 (OR = 2.195; 95% CI: 1.501–3.105; $p<0.001$).

The fourth model included both factors of androgen status (T and DHT level) along with age and SHOKS-COVID score. With a sensitivity of 61.9%, the absence of the association of T and/or DHT, as well as age on unfavorable COVID-19 course, was found as well. Again, the only significant factor that determined the risk of admitting the ICU or death of men with COVID-19 was SHOKS-COVID score (OR=2.12; 95% CI: 1.550–3.156; $p<0.001$).

In the next step, a linear regression model was constructed to predict the association between T levels and SHOKS-COVID as the most sensitive age-adjusted predictor for COVID-19 outcomes (*Table 4*).

This model showed that an increase in T level is associated with a decrease in SHOKS-COVID. Thus, as we mentioned earlier, two variants of associations can be assumed: either a more severe course of COVID-19 was accompanied by a decrease in T level, or, less likely, on the contrary, with a decrease in androgenic function and T level, the severity of COVID-19 increases, as well as SHOKS-COVID score. Of note is the low level of adjusted R2 (0.105), indicating that only 10.5% of SHOKS-COVID variability can be explained by age and T levels.

Discussion. The molecular basis of gender differences in susceptibility to COVID-19 is still under discussion. Even prior to COVID-19, it was known that the reactions of innate and acquired immunity in men and women differ, which is associated with genetic characteristics, particularly the presence of two X chromosomes in women and one X chromosome in men [18]. The X chromosome contains genes responsible for many innate immune responses. Some studies show that the second X chromosome in women can avoid inactivation, resulting in women receiving a double dose of specific genes, thus providing a stronger immune response [2]. On the other hand, X-chromosome-associated synthesis of testosterone in men and its conversion into DHT may be accompanied by activation of androgen receptors, increased activation

Таблица 4

Линейная регрессионная модель для прогнозирования баллов по ШОКС-КОВИД

	B	*p*
T	-0,444	0,005
Возраст	0,045	0,011
Скорректированный (Adjusted) R2=0,105		

of ACE-2 and TMPRSS2, which are the "entrance gates" for the SARS-CoV-2 virus into cells [4]. In this case, an increased level of DHT can be considered as the main negative factor in the development of COVID-19 in men. From this point of view, it can be assumed that early specific or non-specific antiandrogen therapy can reduce the risk of developing COVID-19 and prevent its progression [9, 19]. It should be noted that there are currently no RCT data to support this assumption.

The aim of our study was to analyze the potential association of both T and DHT levels with the severity and prognosis of an COVID-19 requiring hospitalization.

In our previous work, we found a significant association between lower T levels and more severe COVID-19 in men [5]. However, the direction of these associations raised questions. In this study, it is convincingly confirmed that almost half of men (46.4%) with severe and moderately severe course of COVID-19 had low T levels. Patients with COVID-19 with T level below the median were much more likely to be admitted to the ICU (23.7 vs 9.3%; p=0.018) and significantly more likely to require mechanical ventilation (15.8 vs 4.0%; p=0.032) compared to men with T level above the median, respectively. Similarly, a number of other studies have shown that T level in men on mechanical ventilation was 3 times lower than in men without mechanical ventilation [20]. At the same time, logistic regression models didn't show a significant association between the risk of admission to the ICU and the need for mechanical ventilation.

The protective effect of androgens, in particular T, against inflammation in the lung parenchyma was shown earlier, mainly in bronchial asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and various infectious diseases [21]. Our data were also confirmed in other studies: COVID-19 was characterized by the highest T level in men without lung involvement, but it is progressively decreased with damage to the lung tissue of less than 50% and even more with damage to more than 50% of the parenchyma [22]. The development of pneumonia in patients with COVID-19 was also associated with a decrease in T level [23]. For men with COVID-19 admitted to the ICU, T level was significantly lower than for men treated in regular wards [22, 24]. The protective potential of T can be explained by its anticytokine effects: an increased level of T is accompanied by a decrease in interleukin-1β, interleukin-6 [25], as well as an increase in the level of interleukin-10. contributing to a decrease in the level of tumor necrosis factor-α [26], which once again confirms our data and explains the possible mechanisms.

To identify the possible relationships between low T levels, severity of symptoms, and poor prognosis (ICU admission or death) in men with COVID-19, directed acyclic graphs were constructed, as presented in *fig. 1*. As follows from the results of the multivariate analysis (*model 1* in *Table 3*), T level, as well as the age, was not significantly associated with poor prognosis, and high SHOKS-COVID score was a main factor in the admission of patients to the ICU or death. This is explained by the fact that the scale itself covers both clinical (respiratory rate, temperature, saturation, ventilation) and laboratory and instrumental data (CRP, D-dimer, lung damage on CT), which is especially important when predicting the course of the disease. This model has a sensitivity of 57.1% and assumes the leading role of SHOKS-COVID in prognosis and an insignificant additional role of a reduced T level, which is associated not with age, but with the severity of COVID-19 (green dotted arrow in the figure).

To investigate a possible inverse relationship, in which a low level of T determines a more severe course of the disease and SHOKS-COVID score serves as a mediator of the impact on the prognosis, a multivariate model without including an integral scale (model 2 in *Table 3*) was created. In this situation, both lower T level and an advanced age were significantly associated with an unfavorable prognosis. However, the sensitivity of this model was extremely low (only 4%), therefore, low T level is not the main factor of worsening the course of COVID-19 and the increase in SHOKS-COVID score.

Similar data on DHT are very limited, and the available publications suggest only an indirectly the possible relationship with the severity of course and prognosis. In the only study with a low number of patients that compared DHT in men with COVID-19 in the ICU and healthy volunteers, reduced DHT levels were reported in 17 of 35 (48.6%) of patients [27]. An analysis of an expanded sample showed that for patients with COVID-19 in the ICU (n=39), DHT level was significantly lower than in the control group of healthy volunteers and was below the reference values [14]. These patients had a critically severe COVID-19 and were treated in the ICU. Our study included patients with moderate to severe disease who were in the hospital, of which only 25 (16.6%) patients required admission to ICU. In this group, DHT level was within the normal range in 85.6% of patients. The severity of COVID-19 according to SHOKS-COVID score, the rate of admission to the ICU, the length of hospital stays for men with DHT levels below and above the median did not differ. Based on multivariate analyzes, DHT level did not influence on the prognosis in patients with COVID-19. DHT does not affect the outcome of COVID-19, although it may have a negative pro-inflammatory effect [28]. The results of correlation analysis (for DHT and CRP r=0.215; p=0.016) also do not rule out a minor pro-inflammatory effect that was not associated with worsening disease. The most significant factor influencing the likelihood of admission to the ICU of hospitalized men with COVID-19 was SHOKS-COVID score.

A multivariate linear regression model showing an association of SHOKS-COVID with T and age of patients was constructed. An association of SHOKS-COVID scores with T (B: 0.444, p=0.005) was found. The more severe the course of COVID and higher SHOKS-COVID score, lower T level was detected. It should be noted that this model described only 10.5% of SHOKS-COVID variability, which further emphasizes that age and T level are not are the main indicators that determine the severity of COVID-19.

Conclusion. SHOKS-COVID score is the most sensitive predictor of outcomes in hospitalized COVID-19 men, even when adjusting for age. Serum T and DHT level do not directly affect outcomes. The greater severity of the infection and the increase in SHOKS-COVID score are associated with a decrease in T level, a weakening of its anti-inflammatory and anti-cytokine effects, which indirectly worsens the prognosis of hospitalized men with a new coronavirus infection. There is no such a relationship for DHT.

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COMPARATIVE STUDY OF THE EFFICACY AND SAFETY OF A NEW GENERATION OF THULIUM FIBER LASERS FOR URETEROSCOPY AND LITHOTRIPSY

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Introduction. The development and implementation in clinical practice of a 3rd generation thulium fiber laser with the possibility of computer control (modulation) of the shape, amplitude and pulse repetition rate opens up new possibilities for thulium fiber laser lithotripsy.
Aim. To carry out a comparative study of the efficacy and safety of thulium fiber laser lithotripsy using a of the 2nd (FiberLase U3) and 3rd generation devices (FiberLase U-MAX).
Materials and methods. A total of 218 patients with solitary ureteral stones, who underwent to ureteroscopy with lithotripsy using 2nd and 3rd generation thulium fiber lasers (IRE-Polus, Russia) from January 2020 to May 2022 with the same peak power (500 W), laser settings of 1 joule, 10 Hz and with a laser fiber diameter of 365 μm, were included in the prospective study. For lithotripsy using FiberLase U-MAX laser a new original modulated pulse, which was found and optimized in a preclinical study, was used. Depending on the laser, the patients were divided into 2 groups. In 111 patients, stone fragmentation was performed on FiberLase U3 (2nd generation), while 107 patients were undergone to lithotripsy on a new laser device FiberLase U-MAX (3rd generation). Stone size ranged from 6 mm to 28 mm (11±4 mm). The duration of procedure and lithotripsy, the quality of the endoscopic picture during fragmentation (from 0 to 3 points, 0-bad, 3-excellent), the frequency of retrograde migration of stones, as well as damage to ureteral mucosa (of 1-3 degrees) were evaluated.
Results. The time of lithotripsy was significantly lower in the group 2 than in the group 1 (12.3±4.6 vs. 24.7±6.2 min; $p<0.05$). The average quality of the endoscopic picture was significantly better in the group 2 (2.5±0.4 vs. 1.8±0.2 points; $p<0.05$). Clinically significant retrograde migration of stone or its fragments (the need for additional ESWL, flexible ureteroscopy) was noted in 16% vs. 8% of patients in group 1 and 2, respectively ($p<0.05$). Damage to ureteral mucosa of the 1st and 2nd degree due to laser exposure in the group 1 was noted in 24 (22%) and 8 (7%) cases, compared to 21 (20%) and 7 (7%) cases in group 2, respectively. Stone-free state was 84% in group 1 and 92% in group 2.
Conclusion. Modulation of the laser pulse shape allowed to improve endoscopic visibility, increase the speed of lithotripsy, reduce the frequency of retrograde stone migration without increasing the trauma to ureteral mucosa.

K e y w o r d s: ureteroscopy, thulium fiber laser, holmium laser, pulse shape

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Introduction. The implementation of the thulium fiber laser into clinical practice has significantly changed approaches to the treatment of patients with ureteral stones [1–7]. In the Russian Federation, two generations of thulium fiber lasers are currently widespread, including FiberLase U1, U2 and U3. The first generation (U1) was intended for procedures on soft tissues, as it provides a continuous-wave mode with the ability to turn to a pulsed mode. However, energy power in a pulse mode was limited and didn't exceed the power in the continuous-wave mode. For FiberLase U1, peak power was 120 watts. The low price of the laser, its portability, sustainability and low maintenance costs quickly made it very popular among urologists. Increasingly, urologists began to use the ablation mode for the treatment of ureteral stones, as well as in kidney and bladder ones, despite the obvious disadvantage of a long fragmentation time.

To overcome this situation, the developer of a thulium fiber laser (LLC NTO IRE-Polyus, RF) proposed a

fundamentally new 2nd generation thulium lasers (FiberLase U2, U3), which can operate in a high-power pulsed mode (SuperPulse), in which the peak power is many times higher than in continuous mode, reaching up to 500 W, which is quite enough not only for fragmenting stones, but also for procedures on soft tissues (enucleation of benign prostatic hyperplasia, en-bloc resection of a bladder tumor, etc.) [2]. Lasers of the 1st and 2nd generations now have the ability to change the pulse length over a wide range (0.2–66 msec), which is not available in Ho:YAG lasers (0.05–1.5 msec). We presented the comparative advantages of lithotripsy using the 2nd generation thulium fiber laser FiberLase U2 and 3 in 2018 [5]. The worldwide adoption of this device took place after the appearance on the market of thulium fiber laser devices from Olympus. Soltive Premium has identical characteristics with the FiberLase U3 (U3), and Soltive Pro has identical characteristics with the FiberLase U2 (U2) [3]. Since 2018, a large number of comparative studies on the clinical efficacy and safety of SuperPulse thulium fiber lithotripsy have been published [5–7]. U2 differs from U3 in a lower maximum average power (40 W vs. 60 W), which is not always sufficient for high-quality hemostasis when working with soft tissues and in some cases is not enough for effective fragmentation of a stone with a predominance of a protein matrix.

In the latest 3rd generation thulium fiber laser (FiberLase U-MAX), the power was increased, it became possible to set individual settings for lithotripsy modes, and most importantly, it became possible not only to change the length, but also to create a certain pulse shape. In particular, special pulse shapes have been developed for more efficient lithotripsy and enucleation. The minimal effect of all thulium fiber lasers has been proven in numerous experimental and clinical studies [1, 3, 7, 9–11].

Aim. To carry out a comparative study of the efficacy and safety of thulium fiber laser lithotripsy using a of the 2nd (FiberLase U3) and 3rd generation devices (FiberLase U-MAX).

Materials and methods. A total of 342 patients were undergone to ureteroscopy with lithotripsy using a thulium fiber laser on the basis of the urological clinic of the City Clinical Hospital named after. D. D. Pletnev from January 2020 to May 2022, of which 218 were included in our prospective study. Exclusion criteria were standard contraindications to ureteroscopy (acute pyelonephritis, severe bacteriuria), as well as a usage of stone extraction or other modes of fragmentation during lithotripsy. In addition, patients with multiple ureteral stones were excluded. Depending on the laser used, all patients were divided into two groups. In the first group (n=111) U3 was used. The remaining 107 patients were included the second group, in which stone fragmentation was performed with a new generation FiberLase U-MAX device. To carry out a correct comparison, we chose the same levels of laser peak power (500 W), fibers of the same diameter of 365 μm and the same levels of average laser power of 10 W (1 J, 10 Hz). The main difference was the pulse shape: U3 provided a standard rectangular pulse, while in the U-MAX a new original modulated pulse that was developed in a preclinical study, was used.

The procedure time was calculated from the passing the ureteroscope to the stone and includes fragmentation (dusting) with the extraction of fragments using a forceps (lithotripsy time), subsequent removal of the endoscope and putting of drainage (ureteral catheter, external or internal stent).

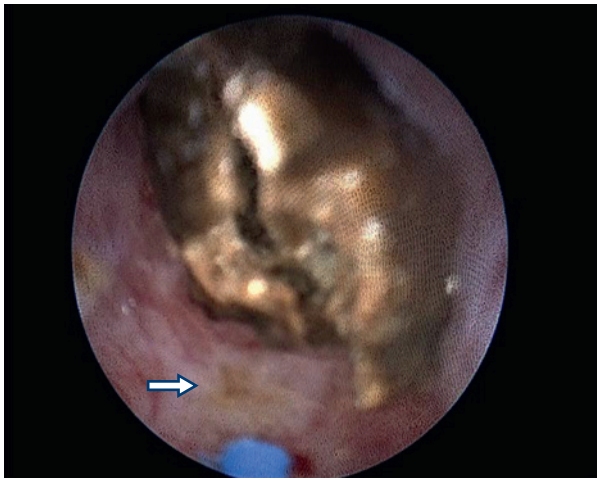

Fig. 1. Endoscopic view of damage to the ureteral mucosa of the 1st degree. A yellow spot in front of the blue laser fiber can be seen (indicated by an arrow)

Ureteroscopy was performed using modern semi-rigid endoscopes from Karl Storz, Richard Wolf, Olympus with a diameter of 8–9 F and a gravity irrigation system (60 cm above the level of the operating table) with a manual pump, which was used to force irrigation in order to improve the quality of the endoscopic picture. All procedures were performed by urologists with extensive experience in lithotripsy.

To assess the quality of the endoscopic picture during lithotripsy, a 4-point scale was used. 0 points meant the absence of visualization, which precluded the lithotripsy and required removal of the endoscope and a significant forcing of irrigation. 1 point was considered in case of worsening of visualization, requiring the cessation of lithotripsy and a slight increase in irrigation, 2 points meant worsening of visualization, making it difficult to fragment the stone and not requiring increased irrigation, 3 points was rated if there was an ideal endoscopic picture without forcing irrigation.

Additionally, the laser effect on the ureteral wall was evaluated when either an unintentional contact of the fiber with the ureteral mucosa occurred, or the laser pulse was directed close to the mucosa. 1st degree damage meant a local discoloration of the ureteral mucosa (*fig. 1*), while in 2nd degree, a small (up to 1 mm) local visible erosion of the ureteral wall without hemorrhage ("caramelized patina") appeared (*fig. 2*), and 3th degree was rated, if erosion with hemorrhage or ureteral perforation occurred.

Preoperative clinical data of patients in both groups are given in *Table 1.*

After the procedure, a ureteral catheter or an external stent was put for 24–48 hours. Thirty-two (28.8%) patients in the first group and 27 (25.2%) patients in the second group had a ureteral stent after lithotripsy. The indications for the internal stent were pronounced changes in the ureter in case of stone impaction and retrograde migration of the stone or its fragments.

Plain urography and ultrasound study were performed to assess the correct position of the drainage and to assess

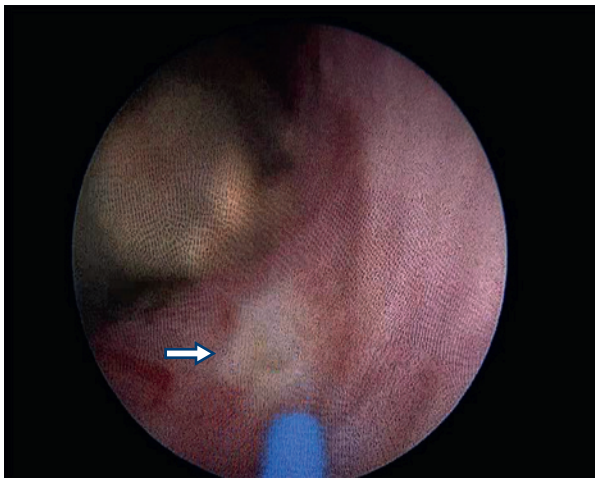

Fig. 2. Endoscopic view of damage to the ureteral mucosa of the 2nd degree. Local erosion of the mucosa without hemorrhage in front of the blue laser fiber can be seen (indicated by the arrow)

the presence of residual fragments. The stent was removed after 4–6 weeks. At the same time, the final evaluation was carried out using ultrasound, plain urography and non-contrast-enhanced tomography.

The study design is shown in *fig. 3*. Automatized statistical processing of the results was carried out using the program Statistica® and Microsoft Excel® application package. When comparing two dependent samples, Fisher's paired t-test was used. The critical level of significance of the statistical hypotheses was taken as a value of less than 0.05, since at this level the probability of a difference between the studied parameters was more than 95%.

Results. Laser lithotripsy was done in all patients. There was no case of stone resistance to laser energy and it was possible to achieve stone fragmentation without changing the selected power parameters. In table 2 the intraoperative characteristics of patients in both groups are given. The first two parameters are of great importance and prove the fact that when using the latest generation of thulium laser, stone fragmentation occurs faster compared to U3. The fragmentation rate and efficiency of lithotripsy are the most important parameters used in preclinical studies to compare different lithotripters. According to our data, the latest generation U-MAX laser provides two times more effective lithotripsy than U3.

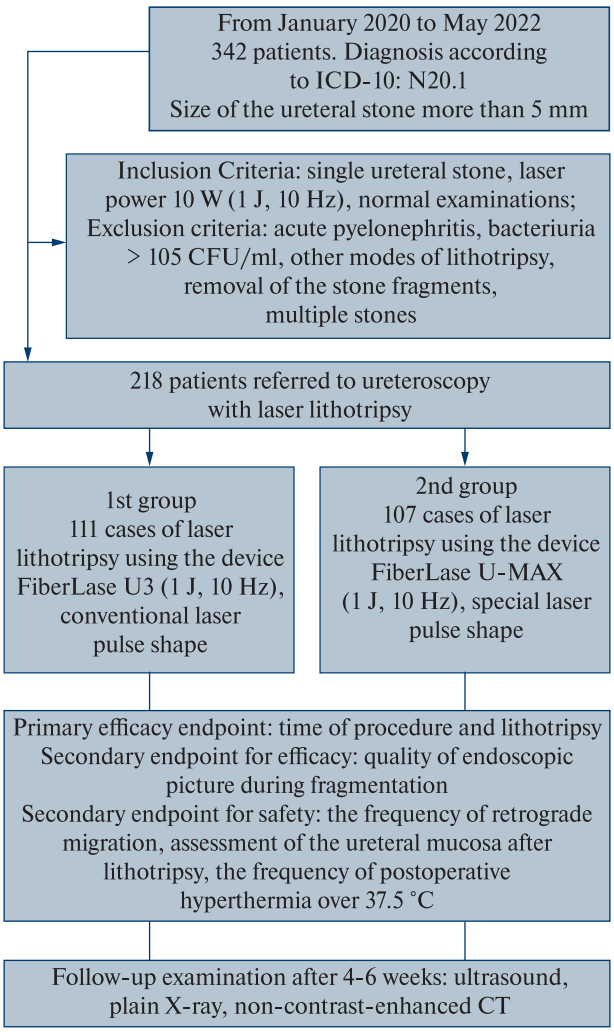

Fig. 3. Study design

In addition to the fragmentation rate, the efficiency is affected by the quality of the endoscopic picture during the procedure. The average quality score of the endoscopic picture was significantly better in the second

Table 1

Baseline characteristics of patients in both groups

Factor	Group 1 (*n*=111)	Group 2 (*n*=107)
Age, years	53±21 (19–82)	51±19 (23–74)
Men (%)	53 (48)	50 (47)
Women (%)	58 (52)	57 (53)
Stone size, mm	11±4 (6–23)	12±3 (8–28)
Stone volume, mm^3	1080±298 (429–2772)	1136±356 (520–2436)
Stone density based on Hounsfield units	1104±325 (634–1612)	1089±312 (602–1586)
Stone below the iliac crest, *n* (%)	62 (56)	56 (52)
Stone above the iliac crest, *n* (%)	49 (44)	51 (48)
Stent, *n* (%)	26 (23)	28 (26)
Nephrostomy tube, *n* (%)	22 (20)	24 (22)

Table 2

Intraoperative results in both groups of patients

Factor	Group 1 (*n*=111)	Group 2 (*n*=107)
Total procedure time, min	35.3±10.6	22.3±8.5
Lithotripsy time, min	24.7±6.2	12.3±4.6*
Fragmentation rate, mm^3/sec	0.7±0.4	1.6±0.7*
Efficiency of lithotripsy, J/mm^3	16.3±4.7	8.1±2.4*
The quality of the endoscopic picture, points	1.8±0.2	2.5±0.4*
Postoperative stenting, *n* (%)	32 (29)	27 (25)

*$p<0.05$ for intergroup differences.

group (2.5±0.4 points) compared to the first group (1.8 ± 0.2 points, $p<0.05$). Further, we assessed the safety of thulium fiber lithotripsy. In *Table 3* the main parameters are presented. The high safety of a thulium fiber laser is shown. Significant differences were achieved only in the rate of retrograde stone migration using the U-MAX device.

Damage to the ureteral mucosa of the 1st and 2nd degrees in the 1st group was observed in 24 (22%) and 8 (7%) cases, compared to 21 (20%) and 7 (7%) cases in the 2nd group, respectively. No grade 3 injuries were found.

The pyelonephritis developed in 14 patients of the first group and in 10 patients of the second group. There was no significant difference between the groups.

At the control follow-up after 4-6 weeks, stone-free rate (SFR) was 84% in group 1 and 92% in group 2. In patients with residual stones, extracorporeal shock-wave lithotripsy or retrograde intrarenal surgery was done. In the late postoperative period, ureteral stricture in the area of lithotripsy was detected in 3 and 2 patients, respectively, which was rather associated with the stone impaction, than effect of the laser energy.

Discussion. Our results indicate greater efficiency of the thulium fiber laser FiberLase U-MAX compared to U3 and comparable safety of both generations of the thulium fiber laser during retrograde ureteroscopy with lithotripsy.

We showed that the possibility of changing the pulse shape allowed to achieve a 2-fold greater efficiency of lithotripsy, which is undoubtedly important when choosing a method for treating large ureteral stones.

The new thulium fiber laser FiberLase U-MAX allows to change the peak power and, in particular, increase it, but in this study, we used the same power characteristics for both lasers. It should be noted that idea of increasing the power of the laser is not new, e.g., there is a gradual increase in the power of the KTP ("green laser") for the treatment of benign prostate hyperplasia. Initially, an 80 W laser machine was developed, then 120 and even 180 W [8]. For lithotripsy, a similar increase in laser power was used to create high-power holmium lasers, which have a power of 80, 100 and 120 W [7]. The purpose of such an increase in power was to expand the possibilities of lithotripsy, which included the destruction of stones in the bladder, ureter, and pelvicalyceal system, either in retrograde or antegrade fashion [9]. Such a variety of stone localizations and clinical forms of the urolithiasis creates certain difficulties in choosing fragmentation modes, and therefore there is a lack of an ideal laser so far. The holmium laser, while having excellent fragmentation capabilities, is less effective in terms of dusting [7]. Holmium lithotripsy takes a longer time when fragmenting large pelvic or ureteral stones [2]. Large energy wastes with a decrease in fiber caliber, as well as a significant propulsion of fragments during fragmentation, are also well-known technical disadvantages of a holmium laser. To overcome these features, the Moses effect was used, the essence of which is to apply a double pulse, when the first one is absorbed by the water in front of the stone in order to vaporize it. This creates a channel for the free passage of the second pulse, which in turn acts directly on the stone. As a result, more effective fragmentation and a decrease in retropulsion occurs, since whole energy of the second pulse is completely absorbed by the stone [7]. Numerous randomized controlled studies have not shown a significant advantage of using this pulse shape compared to a long pulse of a standard shape [12, 13]. All of the above factors determine the relevance of our study, which aims to compare the most popular and widely used model of the U3 with a standard rectangular pulse and the new generation of FiberLase U-MAX thulium fiber laser with the same principle of lithotripsy in combination with novel modulation of the pulse shape.

Two years ago, we carried out a similar study comparing the results of 87 ureteroscopy with lithotripsy using the

Table 3

Evaluation of the safety of thulium fiber lithotripsy in both groups of patients

Factor	Group 1 (*n*=111)	Group 2 (*n*=107)
Retrograde migration of stone (fragments)	18 (16)	9 (8)*
1st degree injury	24 (22)	21 (20)
2nd degree injury	8 (7)	7 (7)
3rd degree injury	–	–
Postoperative hyperthermia > 37.5°C	14 (13)	10 (9)

*$p<0.05$ for intergroup differences.

U3 and a 120 W Lumenis P-120 holmium lithotripter [7]. According to results, U3 was shown to be more efficient than the high-power holmium laser.

Insufficiently effective crushing is a well-known shortcoming of the first generations of thulium fiber laser. Moreover, in the presence of a protein matrix, the fragmentation of the stone in some cases was ineffective due to the "evaporation" of the stone, rather than its fragmentation [10]. The second generation of the thulium fiber laser eliminated this drawback to a certain extent, and the U-MAX modification further expanded the possibilities of stone fragmentation. In our study, there were no cases when thulium fiber lithotripsy was ineffective and a conversion to other methods of intracorporeal fragmentation (holmium, pneumatic, etc.) would be required. Depending on the case, a chemical composition of the stone, the time of stone impaction and a number of other factors, we either fragmented the stone into relatively large particles followed by their extraction, or achieved fine dusting, resulting in punctate fragments, with the same laser settings.

Our sample is sufficiently representative in relation to ureteral stones. Both groups were balanced in terms of the age and gender, stone size, density and localization. The average stone size in both groups exceeded 10 mm in the largest dimension, the volume was about 1100 mm^3, with an average density of more than 1000 HU, i.e., patients in both groups were typical for elective lithotripsy. For grading the stone localization, we used the American classification, according to which a segment above the iliac crest were considered as upper ureter, while a part below this level were allocated to the lower ureter. Both groups had approximately the same proportion of stones with different localization. Obviously, when the stone is located in the upper ureter, its retrograde migration becomes more likely, therefore, the frequency of migration is one of the criteria for the assessment of the efficiency of lithotripsy. For the lower ureter, retrograde migration is less typical, therefore, a balanced composition of both groups is important to exclude the influence of stone localization on the frequency of migration. In our study, a significant difference in the frequency of retrograde migration between the first and second groups was seen (18 [16%] vs. 9 [8%]). One possible explanation is the influence of the shape of the laser pulse in the FiberLase U-MAX, in which the first part of the pulse is optimized to soften the mechanical impact on the stone during the formation of a vapor channel between the distal end of the laser fiber and the stone (Moses's effect). The second part of the pulse is optimized for maximum efficiency of ablation and minimum propulsion. All these properties result in significantly less stone migration compared to U3. It should be noted that retropulsion is, in principle, much less pronounced for thulium fiber lithotripsy compared to holmium laser, which is associated with a more than 4-fold greater absorption of thulium fiber laser energy by water, a longer pulse length, and lower peak power. Nevertheless, the modulation of the laser pulse allows to further alleviate this effect.

It seems that the higher frequency of retrograde stone migration when using U3 is associated both with a greater need for forced irrigation to improve the endoscopic picture during lithotripsy, and with the effect of modulated shape of laser pulse with FiberLase U-MAX on propulsion of the stone or its fragments. Retrograde migration can occur not only due to laser exposure, but also as a result of the movement of the ureteroscope, changes in the position of the operating table, or increased irrigation to improve endoscopic visibility [11]. In most studies, it is difficult to exclude the influence of the above factors; therefore, it is not always correct to allocate a higher or lower retrograde migration rate only to the influence of laser energy [9]. In this regard, the quality of endoscopic visibility during lithotripsy is the most important factor, which ultimately determines the time of the procedure, the comfort of the surgeon and the safety of fragmentation, since damage to the ureter occurs most often due to poor visibility. It should be noted that endoscopic image during holmium and thulium lithotripsy differs [14]. When exposed to holmium energy, the effect of a "snow storm" occurs, which is associated with the laser effect on the surface of the stone and a formation of tiny particles. With thulium fiber lithotripsy, poor visibility may occur as a result of the impact of energy not on the stone, but on the irrigation fluid, with the formation of gas bubbles, so maintaining a contact with the stone is essential to maintain a satisfactory endoscopic picture. However, this negative effect is minimized in U3 and U-MAX thulium fiber lasers.

For laser lithotripsy, good visibility is an important factor. In most studies, this parameter is not evaluated or only the fact that visibility is good or bad is stated [9]. In our study, a visual analogue scale was used to assess endoscopic visibility. At the same time, a significant difference in the average score was found when using FiberLase U-MAX compared with U3. As mentioned earlier, a better endoscopic image results in faster fragmentation, so the faster lithotripsy time with the FiberLase U-MAX is likely a combination of better visibility and more efficient lithotripsy. The last parameter was also significantly higher for U-MAX in comparison with U3.

The fragmentation rate in the group of U3 was 0.7 ± 0.4 mm^3/s versus 1.6 ± 0.7 mm^3/s for U-MAX. A difference in the fragmentation rate is largely associated with the stone composition. An inverse relationship was found for the efficiency of lithotripsy, i.e., to destroy 1 mm^3 of stone, the FiberLase U-MAX device required 2 times less energy (an average of 8.1 ± 2.4 vs. 16.3 ± 4.7 J). These values suggest that the new laser is more efficient. Good endoscopic visibility and high efficiency of lithotripsy allow to change a lithotripsy strategy for impacted and large ureteral stones [2, 4, 6]. More often fragmentation of the ureteral stone is performed from the center towards the periphery, which is associated with an increased likelihood of trauma to the ureteral mucosa at the beginning of the procedure. When using the FiberLase U-MAX, in some cases surgeons started from the periphery to the center of the stone, as this was more convenient.

We have also studied the frequency of laser damage to the ureteral mucosa during lithotripsy. In general, laser energy is safe for the ureter. Clinically significant injuries most often occur during the passage of the guidewire, as a result of forced movement of the ureteroscope or stone extraction, therefore, to assess laser exposure, we developed a special scale by analogy with the classification of ureteral access sheath-associated injuries [15]. The most serious mucosal injury that can be caused by a laser is perforation of the ureteral wall. We didn't observe this complication in any patients. The frequency of damage

to the ureteral mucosa of the 1st and 2nd degrees did not significantly differ in both groups. In addition, there was no increase in the incidence of ureteral strictures in the long-term period.

With laser lithotripsy, especially with impacted ureteral stones, the mucosa may also be affected by laser energy, however, the minimum depth of penetration with a wavelength of 1.94 μm minimizes possible damage to the ureteral wall. Damage to the ureter wall of the 1st and 2nd degrees during lithotripsy in the 1st group was noted in 24 (22%) and 8 (7%) cases compared to 21 (20%) and 7 (7%) in the 2nd group, respectively. No grade 3 injuries were found.

A number of studies have suggested that the increased absorption of laser energy by water during thulium fiber lithotripsy may lead to a greater increase in temperature than with holmium lithotripsy, which requires to control the temperature of the irrigation fluid during stone fragmentation [16, 17]. However, in our study, thermometry of the fluid from the outflow channel in both groups did not reveal a significant increase in temperature. It can be explained by the fact that an increase of temperature is determined by the total laser energy absorbed in the liquid and the irrigation flow rate. The absorption coefficient of a thulium fiber laser by water is 4 times greater than that of a holmium one; therefore, the whole energy is absorbed in a water layer 4 times thinner (about 0.1 mm for a thulium fiber laser vs. 0.4 mm for holmium). However, this layer is much smaller than the dimensions of the kidney, ureter, or bladder, so all energy is completely absorbed in water, and differences in absorption coefficients between thulium fiber and holmium lasers do not matter. In other words, at the same average power of the thulium fiber and holmium lasers and the similar exposure time, an increase in temperature of the water will be the same.

Postoperative hyperthermia above 37.5°C was detected in 14 patients in the first group and in 10 patients in the second. There were no significant differences in the incidence of pyelonephritis in both groups, and the results did not differ from those in earlier publications, despite the shorter procedure time and better imaging in the second group, which didn't require increased irrigation, should allow to decrease a rate of hyperthermia.

Conclusion. In our study, the new thulium fiber laser FiberLase U-MAX showed 2 times higher efficiency and similar safety compared with FiberLase U3 in the treatment of patients with ureteral stones due to the ability to modulate the laser pulse.

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ABOBOTULINUM TOXIN A (DYSPORT®) FOR THE TREATMENT OF NEUROGENIC DETRUSOR OVERACTIVITY

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Increasing of treatment efficiency in patients with neurogenic detrusor overactivity is an important medical and social problem. Its significance is determined not only by the high prevalence of neurogenic lower urinary tract dysfunctions, but also by the high risk of complications, among which an impaired renal function takes the leading place. Botulinum toxin therapy is considered as a second-line treatment and is carried out in case of insufficient efficacy, unsatisfactory tolerability or the presence of contraindications to anticholinergic therapy. Botulinum toxin therapy has been actively used in our country for more than 12 years. In 2022, abobotulinum toxin A (Dysport®) was registered in the Russian Federation for the treatment of neurogenic detrusor overactivity. An overview of the results of clinical trials of Dysport®, indicating its high efficacy and favorable safety profile, is presented in the article. The availability of botulinum toxin in the arsenal of a urologist, which has a high efficiency, opens up additional prospects for the treatment of patients with a neurourological profile.

K e y w o r d s: *neurogenic detrusor hyperactivity, botulinum toxin therapy, botulinum toxin, abobotulinum toxin, Dysport®*

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Neurogenic dysfunction of the lower urinary tract (NLUTD) represents disorders associated with bladder storage and/or emptying, which develop as a result of neurological diseases [1]. The significance of NLUTD is due to their high frequency, a significant deterioration in the quality of life, the risk of developing severe, often life-threatening complications, and a significant economic burden on the healthcare [2]. According to an expert assessment, there are about 910 thousand patients with NLUTD in the Russian Federation, and the current economic costs of their treatment amount to 84.9 billion rubles [3].

Neurogenic detrusor overactivity

One of the most common urodynamic diagnoses in patients with NLUTD is neurogenic detrusor overactivity (NDO), characterized by involuntary detrusor contractions during the filling phase [4]. Clinically, NDO is manifested by neurogenic overactive bladder (OAB), the symptoms of which include urgency with or without urge incontinence, usually in combination with increased daytime and nighttime urination in the absence of urinary tract infection or other overt non-neurological diseases [4]. Urgent urinary incontinence is a common clinical manifestation of NDO. A. Ruffion et al. published a meta-analysis (2013), showing that urinary incontinence due to NDO develops in more than half of patients with spinal cord injury (SCI; 52%) and multiple sclerosis (51%) [5]. Epidemiological data suggest a high prevalence of these disorders, reaching 280–316 and 800 per 1 million adults, respectively [2, 6, 7], which indicates the relevance of the problem.

Symptoms of OAB, and primarily urge incontinence, have an extremely negative impact on the quality of life [8]. It has been established that neurogenic OAB has a more pronounced negative impact on the quality of life than the idiopathic OAB [9].

The most important aspect of NLUTD in general and NDO in particular is the high risk of complications, among which the most significant is upper urinary tract damage. The main risk factor is an increase in intravesical pressure, a decrease in the bladder compliance and capacity [10]. It has been established that NDO develops more often in patients with neurological diseases involving the suprasacral regions of the central nervous system (CNS) [11]. Thus, in those with SCI, NDO is detected in 65% of cases with trauma to the cervical region compared to 78% and 49% patients with involvement of the thoracic region and lumbar region, respectively [12]. The NDO is diagnosed in 65% patients with multiple sclerosis, 45-93% with Parkinson's disease and 35-56%

with multiple system atrophy [12, 13]. A combination of NDO and detrusor-sphincter dyssynergy, which develop in those with suprasacral lesions, is associated with the highest intravesical pressure, as well as a risk of developing upper urinary tract complications.

Pharmacotherapy of neurogenic detrusor overactivity

For the treatment of different types NLUTD, including NDO, the main objectives are to protect the upper urinary tract, to restore the function of the lower urinary tract, to ensure urinary continence or to control urinary incontinence, which should ultimately lead to an improvement in the quality of life [1, 14]. The preservation of kidney function is considered as a priority goal when planning treatment strategy in patients with NLUTD. In this case, the leading importance is given to maintaining the detrusor pressure within safe limits both during the filling and emptying phases. High maximum detrusor pressure in the emptying phase (>80 cm H_2O in men and >60 cm H_2O in women), high detrusor leak point pressure (>40 cm H_2O), low bladder compliance (<20 ml/sec H_2O), a decrease in maximum cystometric capacity (<200 ml) and an increase in postvoid residual (>100 ml or more than 30% of the functional bladder capacity) are all independent risk factors of upper urinary tract damage [15, 16].

Anticholinergic therapy is the first line of treatment for patients with NDO [17–19]. Antimuscarinics prevent the activation of M-cholinergic receptors by the neurotransmitter acetylcholine, reducing the detrusor contractions and increasing the functional bladder capacity [17, 20. 21]. The bladder contains two subtypes of M-cholinergic receptors, M2- and M3-, and the density of M2 receptors is approximately 4 times higher than that of M3 receptors [22]. In healthy people and patients with idiopathic urinary tract dysfunction, detrusor contractions are provided by the activation of M3-cholinergic receptors. However, with NLUTD there is an increase in density and, most importantly, a change in the function of M2-cholinergic receptors [23]. There is an increase in number of muscarinic receptors, which are involved in detrusor contractions along with M3-cholinergic receptors [23]. As a result, the standard doses of anticholinergic drugs in patients with NDO is often ineffective. These patients are recommended to take M-anticholinergics in higher doses, and a combination of two drugs with antimuscarinic activity is also used [14, 24]. Thus, a high frequency and severity of side effects when prescribing anticholinergic therapy to patients with NDO is often seen. The ability of most antimuscarinic drugs to penetrate the blood-brain barrier is of importance for neurological patients, since it causes CNS side effects, including cognitive dysfunction, memory impairment, drowsiness, confusion, and emotional lability [25, 26]. Insufficient efficiency of anticholinergic therapy at usual doses and high frequency and severity of side effects with increased dose determine the relatively low adherence of patients with NDO to therapy compared with those with idiopathic detrusor overactivity. Thus, A. Manack et al. (2011) studied in a retrospective study the medical records of 26,922 patients with NLUTD and found that 38% of them refused anticholinergic therapy during the first year of treatment [27].

Neurological patients often present with a combination of NDO and detrusor-sphincter dyssynergy. In these cases, along with high intravesical pressure, a large postvoid residual is also usually seen, which extremely affects the function of the upper urinary tract. To reduce intravesical pressure and ensure bladder emptying, such patients received anticholinergic drugs in combination with intermittent self-catheterization, usually 4–6 times a day [28].

A number of publications showed the efficiency of prescribing selective β3-agonists to patients with NDO [29]. However, these drugs are not yet included in the guidelines for the treatment of NLUTD, mainly due to the insufficient data, especially with a long-term follow-up.

In cases of inefficiency of oral drugs for NDO, it is considered refractory (resistant). Currently, there are no clear criteria for the refractory NDO. At the same time, unlike idiopathic detrusor overactivity, in which one may find an optimal regimen for prescribing long-term anticholinergic drugs and focus on the clinical manifestations, in patients with NDO, urodynamic criteria, particularly the intravesical pressure, are of importance. Therefore, it is necessary to consider NDO as refractory, if there is no normalization of intravesical pressure, while taking antimuscarinics [14]. Due to the fact that patients with NDO have a high detrusor pressure during the filling phase and a significant risk upper urinary tract damage, the identification of refractory NDO and the appointment of the second-line treatment, botulinum therapy, should be carried out much faster than in the idiopathic detrusor overactivity [1, 14].

Botulinum therapy: general principles and application in urology

Indications for botulinum therapy in patients with NDO are insufficient efficacy and/or poor tolerability of anticholinergic drugs, as well as the presence of contraindications [1, 14]. Despite the name, botulinum therapy is a minimally invasive surgical method that involves injection of botulinum toxin into the bladder wall. Botulinum toxin is a protein-based neurotoxin produced by the gram-positive spore-forming anaerobic bacteria Clostridium botulinum, which is one of the most powerful neurotoxins in the nature: even 1 ng (10^{-9} g) of this substance exhibits biological activity [30].

Depending on the antigenic properties, 7 variants (serotypes) of botulinum toxin are distinguished. The seven main types of botulinum toxin are named types A to G (A, B, C, D, E, F and G). The most widely used in medicine is botulinum toxin type A (BTA). The latter is a protein with a molecular mass of about 150 kDa, which consists of two subcomponents, light (50 kDa) and heavy (100 kDa) chains connected by disulfide and non-covalent bonds [31]. The neurotoxic effect of BTA is based on its ability to cleave the membrane protein SNAP-25 (synaptosomal-associated protein), which ensures the connection of the synaptic vesicle with the presynaptic membrane of the cholinergic neurons. Cleavage of SNAP-25 blocks the release of the neurotransmitter acetylcholine into the synaptic gap and leads to persistent denervation of muscle fibers. When BTA is introduced into the detrusor, its contractile activity is inhibited [32].

Botulinum therapy has been successfully used in many areas of medicine since the early 1990s. It is especially widespread in neurology (various forms of spasticity, cervical dystonia, blepharospasm, etc.) and

cosmetology. The first report on the use of botulinum therapy in urology dates back to 1988, when D. Dykstra et al. presented the results of the successful use of BTA in patients with detrusor-sphincter dyssynergy [33]. In 2000, B. Schurch et al. used BTA for the first time with positive results in patients with NDO [34]. Subsequently, multicenter clinical trials have confirmed the efficiency of botulinum therapy in patients with neurogenic and idiopathic detrusor overactivity, overactive bladder and urge incontinence [35, 36]. Based on their results, Botox has been included in national and foreign clinical recommendations as a second-line treatment in case of inefficiency or intolerability of oral pharmacotherapy [1, 14]. Currently, botulinum therapy is used in clinical practice for the treatment of idiopathic and neurogenic detrusor overactivity [37–39]. In the Russian Federation, botulinum therapy has been actively used in urology for more than 12 years. According to the literature, when botulinum therapy is carried out for a long period, its efficiency does not decrease, and the treatment tolerance does not worsen [40]. Both in our country and abroad, the efficiency of long-term botulinum therapy is being studied, and more and more experience has been gained in such urological diseases as detrusor-sphincter dyssynergia [41], chronic pelvic pain syndrome/interstitial cystitis [42, 43], benign prostatic hyperplasia [44], and erectile dysfunction [45].

Abobotulinum toxin A (Dysport®) in the treatment of NDO

For the treatment of urological diseases, two variants of BTA are used, known under the non-proprietary international names "abobotulinum toxin" and "onabotulinum toxin". BTA subtypes differ mainly in proteins surrounding the active substance, namely the neurotoxin itself. Under natural conditions, BTA is synthesized in the form of a protein-containing complex, which has an active component, particularly botulinum neuroprotein (active neurotoxin), whose molecular weight is 150 kDa, and special non-toxin proteins (NAPs) with a molecular weight of 350 to 750 kDa, depending on a specific manufacturer. In addition, BTA preparations also includes additional compounds that act as stabilizers. Under the physiological conditions (pH=7.4, when dissolved with a normal saline in a vial), the neurotoxin complex dissociates, resulting in the separation of the active part (neuroprotein with the molecular weight of 150 kDa) and NAPs [46].

For a long time, the only BTA licensed for the treatment of urological diseases was onabotulinum toxin. In 2011, FDA approved it for the treatment of urge urinary incontinence due to detrusor overactivity. Later, national regulatory authorities in many other countries, including the Russian Federation, registered onabotulinum toxin for this indication.

Another drug, abobotulinum toxin A (AboBtA), marketed under the trade name Dysport® (Ipsen, France), was first approved in 1990 in the UK for the treatment of blepharospasm and hemifacial spasm. Since then, Dysport® has been licensed in more than 90 countries for a variety of indications (focal spasticity in adults and children, cervical dystonia, axillary hyperhidrosis), and its efficacy and safety have been proven in numerous clinical trials. The urological indication for the use of AboBtA is NDO. Long-term studies have demonstrated a high efficacy and a good safety profile of intradetrusor injections of AboBtA at doses from 500 U to 1000 U [47–51]. With the use of AboBtA, positive dynamics of NDO symptoms and a significant improvement in the quality of life was noted. Along with clinical efficacy, there was a significant improvement in urodynamic parameters, including a decrease in maximum detrusor pressure and an increase in maximum cystometric capacity (see table).

In 2018, F. Bottet et al. [53] published the results of a retrospective study of an efficacy of intradetrusor injections of AboBtA in 57 patients with NDO, in whom previous treatment with onaBTA was ineffective. The authors noted a significant decrease in the number of episodes of urinary incontinence per day in 52.6% of patients and an increase in maximum cystometric capacity by 41.2 ml with an average decrease in maximum detrusor pressure by 8.1 cm H_2O. They concluded that most patients with NDO who are not susceptible to onaBTA benefit from subsequent intradetrusor injections of AboBtA.

Aforementioned results of indicate a high efficacy and good tolerability of intradetrusor injections of AboBtA in patients with NDO, but the number of participants was relatively small. The first truly large-scale program for use of AboBtA for NDO was a series of two similarly designed, double-blind, multicenter, randomized phase III trials CONTENT1 and CONTENT2, which involved 485 patients in 131 centers in many countries around the world, including in the Russian Federation [52]. The study included patients with urge urinary incontinence due to NDO associated with SCI (70% of cases) with a lesion level lower T1 or multiple sclerosis (30% of patients) performing clean intermittent self-catheterization. The study consisted of two stages. In the first part, depending on the randomization, patients received intradetrusor injections of AboBtA at a dose of 600 U (n=162) or 800 U (n=161), or placebo (n=162). At the second stage, repeated injections of AboBtA 600 U or 800 U were performed after 12 or more weeks without placebo-control. Retreatment was performed if the number of urge incontinence episodes was reduced by less than 30% from baseline.

Improvement in clinical and urodynamic parameters was noted by 2 weeks after intradetrusor injections. By the 6th week, a significant reduction in the frequency of urinary incontinence episodes per week compared with placebo was found in both AboBtA groups (-22.7 and -23.6, respectively, in 600 U and 800 U vs. -12.7 for placebo). Urgent urinary incontinence was resolved in 36%, 29% and 3% of patients receiving 600, 800 U of AboBtA and placebo, respectively (p<0.001). Patients in both abo-BTA groups showed a significant increase in mean voided volume and I-QOL score compared to placebo, an increase in maximum cystometric capacity, a decrease in maximum detrusor pressure in the filling phase, and an increase in bladder volume at the first involuntary detrusor contraction. At baseline, involuntary detrusor contractions during urodynamic study were detected in all patients, however, by the 6th week they were absent in 44% and 55% of those receiving 600 and 800 U, compared to only 7% of those in placebo group. Regardless of the dose of AboBtA, more than 40% of

Table

Dynamics of urodynamic parameters in patients with NDO after injection of abobotulinum toxin A (Dysport®)

Study	n	Dose of Botox	Mean change in maximum cystometric capacity by 4–6 weeks after injection, ml	Mean change in detrusor pressure by 4–6 weeks after injection, cm H2O
Ruffion A. et al. (2006) [47]	45	500 U	+192	-12
		1000 U	+213	-29
Ehren I. et al. (2007) [48]	31	500 U	+180	-52
Grise P. et al. (2010) [49]	77	500 U	+192	-
		750 U	+243	
Denys P. et al. (2017) [50]	42	750 U 15 injections	+162	-39
		750 U 30 injections	+196	-29
Kennelly M. et al. (2022) [52]	485	Placebo	-4	-4
		600 ЕД	+164	-33
		800 ЕД	+175	-35

patients did not require retreatment for at least 48 weeks after intradetrusor injections at the first stage of the study.

Tolerability of treatment was satisfactory in patients of all three groups and did not significantly differ depending on the drug. The most common adverse event was symptomatic lower urinary tract infection, and there were no significant differences in the frequency depending on the type of treatment. Within 12 weeks after the first injection, lower urinary tract infection was observed in 14%, 15% and 17% of patients receiving 600 U, 800 U of AboBtA or placebo, respectively.

An additional analysis of the results of the CONTENT1 and CONTENT2 trials showed that the efficacy of AboBtA is comparably high in patients with NDO, regardless of the underlying neurological condition [54]. The mean time to repeated injection was somewhat longer in those with multiple sclerosis, who also had a more pronounced dose-dependent effect of AboBtA compared with patients with SCI.

F. Cruz et al. (2023) [55] performed a systematic analysis with an indirect comparison of the efficacy and safety of AboBtA and onabotulinum toxin-A (onaBTA) in patients with refractory NDO due to multiple sclerosis and SCI. The authors reviewed the results of the CONTENT1 and CONTENT2 studies described above and four randomized clinical trials of onaBTA (a total of 1306 patients with NDO). According to the results, 12 and 24 weeks after treatment, patients who received AboBtA at a dose of 800 U had a more pronounced decrease in the frequency of urge incontinence compared with those who received onaBTA at a dose of 200 U.

A number of studies have shown the efficiency of AboBtA in patients with idiopathic detrusor overactivity [56] and detrusor-sphincter dyssynergy [57].

In 2022, AboBtA (Dysport®) was registered in the Russian Federation for the first time for urological indication, namely urinary incontinence in patients with NDO (neurogenic OAB) as a result of SCI (traumatic or non-traumatic) or multiple sclerosis, who perform clean intermittent catheterization. According to the instructions, the dose of Dysport® for the treatment of NDO is 600 U (two bottles of 300 U) or 800 U (one bottle of 300 U and one bottle of 500 U), and it is recommended to inject the drug into the detrusor at 30 points. The use of AboBtA for the treatment of NDO is included in Russian guidelines for the treatment of NLUTD [1].

Publications devoted to the analysis of the content of active neurotoxin in various BTA preparations and the assessment of its potential effect on the duration of the effect are of particular interest. M. Field et al. (2018) calculated the amount of active neurotoxin in each BTA product, particularly AboBtA (Dysport®) and onaBTA (Botox®). According to the test, the following results were obtained: the amount of active neurotoxin in the vial of Dysport® 500 U is 2.69 ng compared to 0.9 ng in the vial of Botox® 100 U. It should be noted that the active units are specific and cannot be compared with those of other preparations containing botulinum toxin, which excludes a direct comparison. At the same time, the content of active neurotoxin, the structure of which is the same for all BTA preparations, at the maximum approved dose allow direct comparison of BTA preparations [58]. Therefore, it is possible to determine the difference in the amount of active neuroprotein, comparing the content of active neurotoxin per the maximum approved dose of drugs for the treatment of NDO. In the preparation Dysport®, its content is 4.3 ng compared to 1.8 ng in Botox®. Achievement of long-term symptom control may be due to a higher level of active neurotoxin in the maximum dose of Dysport® compared to other BTAs [58-60].

Increasing the efficiency of treatment of patients with NLUTD is not only an important urological, but also a significant medical and social problem. The search for new treatment approaches is an urgent task of modern medicine. In this regard, the introduction of botulinum therapy into clinical practice opened a new era in the treatment of bladder dysfunctions. Likewise, the appearance of the drug Dysport® (abobotulinum toxin) in the armamentarium gives additional possibilities for the treatment of NDO. Injections of Dysport® contribute to a long-term, up to 48 weeks, decrease in intradetrusor pressure, elimination of involuntary detrusor contractions and improvement of most urodynamic parameters. The results of clinical trials have shown a high efficacy and good tolerability of Dysport®, which allows us to recommend it for widespread use in the treatment of patients with NDO.

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