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INFLUENCE OF ADDING ZINC ARGINYLE-GLYCINATE TO IMPROVE EFFICACY OF BIOREGULATORY PEPTIDES OF THE PROSTATE GLAND IN TREATMENT OF PATIENTS WITH IMPAIRED SPERM PARAMETERS

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Abstract.

The drug Prostatilen® AC, rectal suppositories were developed on the basis of the previously registered medicine containing bioregulatory peptides of the prostate gland - Prostatilen® rectal suppositories, 3 mg, from whom it differs by the addition of active pharmaceutical ingredient zinc arginyle-glycinate dihydrochloride (ZAG). The aim of this study was to analyze the positive effect of adding ZAG to the drug in patients with impaired spermatogenesis.

A total of 98 men aged 25-45 years (an average of 35.2±4.3 years) with a verified diagnosis of chronic abacterial prostatitis and related reproductive dysfunctions in the phase III, randomized, multicenter, open-label clinical trial was examined. The duration of participation of patients in the study was 14–16 days, the screening period was 2–3 days, the duration of therapy was 10 days, and the final examination was 2–3 days. A study group (n=49) received therapy with Prostatilen AC once daily, a control group (n=49) had Prostatilen once daily. All patients underwent conventional semen analysis before and after treatment. The obtained parameters were compared.

During the analysis of the average statistical data in the comparison groups, it was found that treatment with Prostatilen AC leads to an increase in the total population of motile spermatozoa (cells A + B + C) by 14.3%, and the reference drug Prostatilen contributes to an increase in this indicant by 4.1% compared with the results of a screening examination with significantly higher efficiency in increasing the relative count of spermatozoa with a fast progressive motility (After therapy Prostatilen/Prostatilen AC p=0.0004). Prostatilen AC showed significantly higher efficiency in terms of increasing the count of normal forms of spermatozoa in the ejaculate than the reference drug Prostatilen (After therapy Prostatilen/Prostatilen AC p=0.0118). In patients who received the drug Prostatilen AC the number of abnormal forms of spermatozoa decreased by 12.4% (After therapy – 55.57%), and in the comparison group (drug Prostatilen) by 6.5% (After therapy – 58.90%) with significant decrease in forms of abnormal spermatozoa with head, acrosome, or neck pathology for Prostatilen AC compared to control.

Prostatilen AC compared to Prostatilen had a statistically significant and clinically significantly superior efficacy in relation to initially impaired sperm parameters (improve of sperm motility, restoration of morphologically normal sperm, decrease in forms of abnormal spermatozoa with head, acrosome or neck pathology). This drug could be recommended to use in the treatment of patients in whom chronic prostatitis occurs with concomitant disorders of sexual and reproductive functions.

Key words. Impaired spermatogenesis, zinc arginyle-glycinate, bioregulatory peptides of the prostate gland, chronic prostatitis.

Introduction.

It has been shown that zinc plays a significant role in the male reproductive system [1-4]. The highest concentrations of zinc are found in semen and prostate secretions. Prostate diseases and concomitant sexual and reproductive disorders are zinc-deficient conditions [5]. Against the background of zinc deficiency, there is a delay in sexual development in boys and a decrease in fertility in men [6]. Zinc deficiency leads to a decrease in testicular function, their atrophy, a decrease in the production of sperm, testosterone, and a decrease in potency in men. It has been suggested that Zinc acts as an important anti-inflammatory factor and that it is involved in the sperm's oxidative metabolism [6]. Zinc concentration is high in the seminal fluid and has a multifaceted role in the sperm's functional properties. Zinc ion has been linked with key events in the acquisition of fertilization ability by spermatozoa, including motility, capacitation and acrosomal exocytosis [1].

Arginine reduces the growth of pathogenic microflora, participates in spermatogenesis, improves erectile function, has a significant regulatory effect on the functions of the genitourinary system; ornithine formed from arginine is a precursor of spermine and spermidine [7-9].

Inclusion in addition to the regulatory peptides of the prostate composition of the substance L-arginine (100 mg) and zinc (23 mg) in the form of zinc arginyl-glycinate dihydrochloride (ZAG) active pharmaceutical ingredient (API) made it possible to develop Prostatilen AC drug based on Prostatilen preparation and expand the scope of this medicinal product, using it for the treatment of patients with chronic abacterial prostatitis with impaired reproductive function.

Preclinical studies of Prostatilen AC showed positive results in animal experimental model of male infertility (pathozoospermia) [10] as well as a series of clinical studies [11-14].

The aim of this study was to analyze the positive effect of adding ZAG to the drug in patients with impaired spermatogenesis.

Materials and methods.

A total of 98 men aged 25-45 years (an average of 35.2±4.3 years) with a verified diagnosis of chronic abacterial prostatitis and related reproductive dysfunctions were examined. Inclusion criteria were chronic genitourinary pain in the absence of any infection localized to the prostate gland employing standard methodology with presence of any impaired sperm parameters in semen analysis and erectile dysfunction. Exclusion criteria were intolerance to at least one of the components of the study drugs, infectious or inflammatory diseases, concomitant diseases in the stage of decompensation requiring drug therapy. All patients signed the established informed consent form to participate in the clinical trial. The present clinical trial was carried out in accordance with the principles of the Declaration of Helsinki, the ICH GCP and local ethics committee.

The patients were treated and examined in an outpatient setting at 2 specialized research centers. The duration of participation of patients in the study was 14–16 days, the screening period was 2–3 days, the duration of therapy was 10 days, and the final examination was 2–3 days. A study group (n = 49) received therapy with Prostatilen AC once daily, a control group (n = 49) had Prostatilen once daily. Patients did not receive any other therapy during the treatment period. All patients underwent conventional semen analysis before and after treatment. The obtained parameters were compared.

The investigated drug Prostatilen® AC, rectal suppositories (JSCo Cytomed, Russia) composed of prostate extract (0.03 g) and zinc arginyle-glycinate dihydrochloride (0.18 g as zinc arginyle-glycinate). API zinc arginyle-glycinate dihydrochloride (ZAG; JSCo Cytomed, Russia) contains L-arginine (55,4%), glycine (23,7%) and zinc (20,9%) in form of chelate complex.

The comparison drug Prostatilen® rectal suppositories, 3 mg (JSCo Cytomed, Russia) contain only prostate extract (0.03 g or 3 mg as prostatic peptides).

The analysis of the obtained data was carried out using the IBM SPSS Statistics program 22. In order to test the significance of differences between the samples, Student's t-test was calculated (for paired and independent samples with a normal distribution), as well as the Wilcoxon W-test for paired and Mann-Whitney U-test for independent samples with a non-normal distribution. The normality of distribution in the samples was assessed using the Kolmogorov–Smirnov z-test. The applied significance threshold was taken equal to 95%. The level of achievement of the null statistical hypothesis was $p \geq 0.05$.

Sperm motility grading:
Grade A – rapid progressive motility
Grade B – slow progressive motility
Grade C – Non-progressive motility
Grade D – Immotility

Results.

During the analysis of the average statistical data in the comparison groups, it was found that the study drug Prostatilen AC leads to an increase in the total population of motile spermatozoa (cells A + B + C) by 14.3%, and the comparison drug Prostatilen contributes to an increase in this indicator by 4.1% compared with the results of a screening examination. To assess the level of reproductive activity, subpopulations of spermatozoa with progressive motility (cells A + B) are of the greatest importance. After the treatment, the number of spermatozoa with progressive motility in the control group (Prostatilen) increased by 8.3% (Screening/After therapy - 47.7/51.7), and in the comparison group (Prostatilen AC) by 20.9% (Screening/After therapy - 43.3%/52.4%) and reached the normal values of this indicator. Intragroup differences between the screening and final study of the ejaculate in terms of the count of cells with fast (cells A) and slow (cells B) progressive motility were statistically significant (Screening/After therapy A and B Prostatilen p=0.0284 and p=0.0404, respectively; Screening/After therapy A and B Prostatilen AC p<0.0001and p=0.0009, respectively) (Figures 1a, 1b). During the statistical analysis of the results of the study, it was found that the study drug Prostatilen AC , in comparison with the reference drug (Prostatilen) shows significantly higher efficiency – 3% difference in increasing the relative count of spermatozoa with a fast progressive motility (After therapy Prostatilen/ Prostatilen AC p=0.0004) (Figure 1a).

An increase in the relative count of spermatozoa with progressive motility led to a decrease in the percentage of cells with non-progressive motility (C cells) and immobile forms (D cells) in the ejaculate for both groups. Statistical analysis of the percentage of immobile cells during treatment with study drugs showed that both drugs contributed to a significant decrease in this cell population compared with the results of the screening (Screening/After therapy Prostatilen p=0.0096; Screening/After therapy Prostatilen AC p=0.0008) (Figures 1c, 1d). Both drugs showed similar efficacy in reducing from screening to end of therapy the population of immobile spermatozoa, from 31.75 to 27.10% for Prostatilen and from 33.90 to 29.31% for Prostatilen AC with absence of significant differences between comparison groups.

During the initial examination, the percentage of normal forms of spermatozoa in the comparison groups was reduced and amounted to 38.69% (Prostatilen group) and 32.92% (Prostatilen AC group) respectively (Figure 2). After treatment with the study drugs in both groups, a significant increase in the relative count of normal spermatozoa was noted (Screening/After therapy Prostatilen p<0.0001; Screening/After therapy Prostatilen AC p<0.0001) – 42.2% and 43.12%, respectively. The drug Prostatilen AC showed significantly higher efficiency in terms of increasing the count of normal forms of spermatozoa in the ejaculate than the reference drug Prostatilen as evidenced by the presence of statistically significant differences between comparison groups (After therapy Prostatilen/Prostatilen AC p=0.0118) (Figure 2).

During the initial examination (Screening), the relative number of abnormal spermatozoa in the comparison groups was almost the same (62.47% in the main group - the drug Prostatilen AC and 62.78% in the control group - the drug Prostatilen). Treatment with the study drugs revealed a similar trend of a decrease in the overall population of abnormal spermatozoa. In patients who received the drug Prostatilen AC rectal suppositories, the number of abnormal forms of spermatozoa decreased by 12.4%, and in the comparison group (drug Prostatilen) by 6.5%.

The registered drug (ProstatilenAC) and the reference drug (Prostatilen) significantly reduced the percentage of cells from

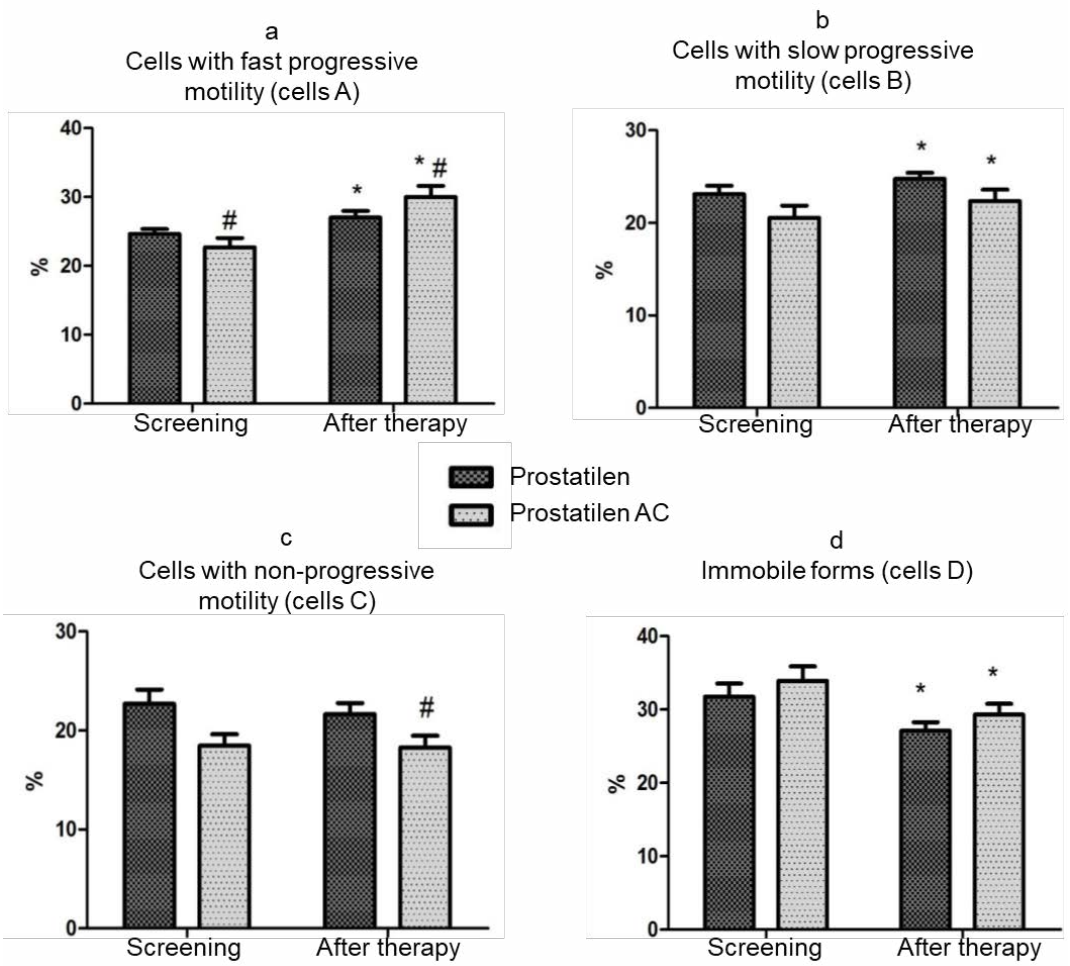

Figure.1. Change in relative sperm count with fast (a) and slow (b) progressive motility, non-progressive motility (c) and immobile forms (d) in the comparison groups before treatment (Screening) and 2-3 days after treatment drugs Prostatilen and Prostatilen AC.

**- p<0.05 compared with screening results, #- p<0.05 compared with Prostatilen after therapy.*

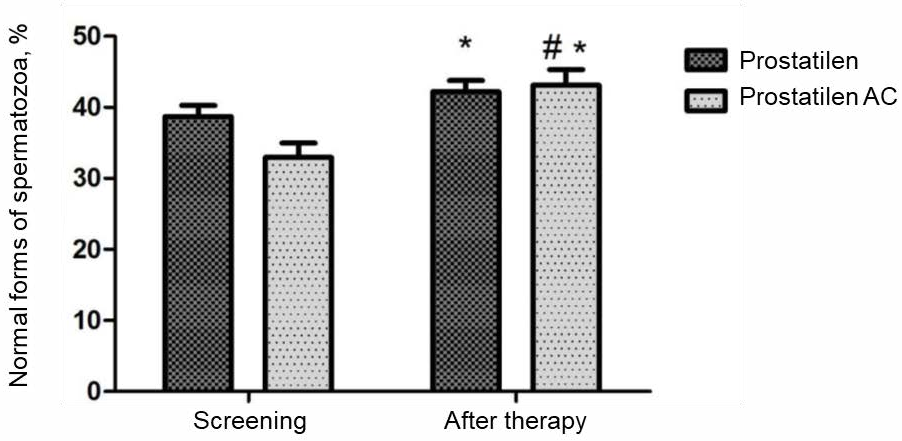

*Figure. 2. Change in the relative count of normal spermatozoa in the comparison groups during treatment with study drugs. *- p<0.05 compared with screening results, #- p<0.05 compared with Prostatilen after therapy.*

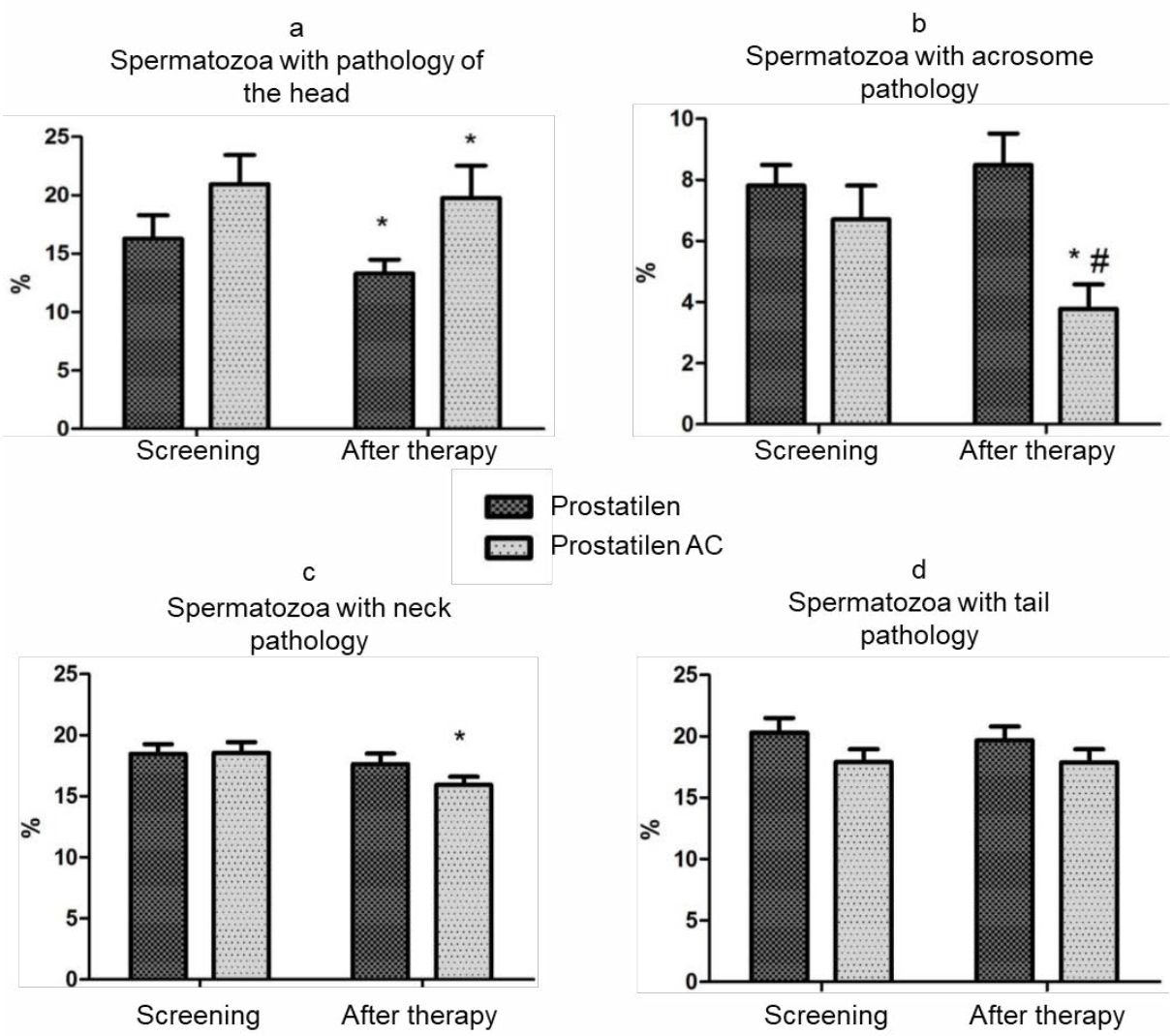

Figure. 3. Change in the relative count of spermatozoa with the pathology of the head (a), acrosome (b), neck (c), tail (d) in the comparison groups during treatment with study drugs.

**- p<0.05 compared with screening results*

#- p<0.05 compared with Prostatilen after therapy.

head pathologies after course use (Screening/After therapy Prostatilen p=0.0096; Screening/After therapy Prostatilen AC p=0.0008). There were no significant intergroup differences in the percentage of spermatozoa with head pathology during the final study of the ejaculate (Figure 3a).

During the analysis of the clinical trial data, it was found that the drug Prostatilen did not have a significant treatment effect on the relative count of spermatozoa with acrosome pathology (Screening/After therapy p=0.9084) (Figure 3b). The use of the study drug Prostatilen AC contributed to a statistically significant decrease in the population of spermatozoa with acrosome pathology in the ejaculate of patients of the main group during the final study compared with the results of screening (Screening/After therapy p<0.0001). Statistical analysis of data from the baseline (Screening) showed that in terms of the relative count of spermatozoa with acrosome pathology in the ejaculate, the comparison groups did not have statistically significant differences and were representative (Prostatilen group - 7.8%, Prostatilen AC group - 6.7%, p=0.0530). Statistical evaluation of the intergroup dynamics of the count of cells with pathological changes in the acrosomal region, during treatment with the studied drugs, showed that Prostatilen AC appeared significantly more pronounced efficacy (3.8%) than the reference drug Prostatilen (8.5%) contributing to the reduction of this population of pathological spermatozoa (After therapy Prostatilen/ Prostatilen AC p<0.0001), which may serve as indirect evidence of an increase in reproductive function (Figure 3b).

According to the average value of the relative count of spermatozoa with neck pathology during the screening examination, the groups did not have significant differences. In the treatment with the study drugs in the comparison groups, similar trends to a decrease in the percentage of spermatozoa with pathological changes in the neck in the ejaculate were revealed. The dynamics of the relative count of cells with pathology of the neck, during the treatment with the drug Prostatilen AC

was characterized by a significant decrease in this population of spermatozoa (Screening - 18.55% / After therapy - 15.92%, $p<0.0001$) at the final examination patients, compared with baseline data (Figure 3c). In the control group (Prostatilen), the decrease in the count of this cell population was less pronounced (Screening - 18.40%/ After therapy -17.60%) and was not significant ($p=0.13$). Registered drug Prostatilen AC showed greater efficiency in reducing spermatozoa with neck pathology in the ejaculate than the reference drug Prostatilen.

Analysis of the screening examination data showed that the comparison groups in terms of the relative count of spermatozoa with pathological changes in tail were representative and had a normal intragroup character of the distribution of indicators. Evaluation of the intragroup dynamics of the percentage of cells with abnormal tail morphology during treatment did not reveal the effect of the studied preparations on this indicator. As a result of statistical processing of data from a clinical study, no data were obtained on the presence of intra- and intergroup differences in the relative count of spermatozoa with tail pathology in the ejaculate during treatment with the studied drugs (Figure 3d). Thus, in the course of the clinical study, it was shown that the preparations Prostatilen AC and Prostatilen did not have a significant effect on the maintenance of the spermatozoa population with tail pathology.

Discussion.

Impaired sperm motility is one of the main factors in male infertility. Cell motility depends on the secretory activity and condition of the prostate gland. Due to the fact that the prostate extract (the main active component of the studied drugs) has an organotrophic effect (reduces the degree of edema, leukocyte infiltration, normalizes the secretory function of prostate epithelial cells), one of the predicted effects of the studied drugs was considered their effect on the increase in the population of mobile spermatozoa, and in the registered drug Prostatilen AC due to the presence of arginine, glycine and zinc in its composition, this effect should be more pronounced.

One of the important indicators of the semen analysis is the assessment of the morphological structure of spermatozoa. With a decrease in the number (both absolute and relative) of normal spermatozoa, due to various disorders of spermatogenesis, natural fertilization becomes problematic. Defective spermatogenesis and some forms of epididymal pathology are often associated with an increased number of abnormal spermatozoa. Morphological defects are often combined. The abnormal spermatozoon usually has a reduced fertilizing potential, depending on the type of anomaly, and may also contain abnormal DNA. Morphological defects are associated with increased DNA fragmentation, increased risk of structural chromosomal aberrations, immature chromatin, and aneuploidy. That is why the main emphasis is placed on the shape of the sperm head, although the pathology of the flagellum (its middle and main parts) is also considered as an aspect of reduced fertility).

Zinc deficiency is one of the main etiological factors contributing to spermatogenesis disorders. This is confirmed by the fact that many reproductive and sexual disorders have been eliminated against the background of the additional appointment of this microelement. The simplest and most objective method for assessing the morphology of spermatozoa is recommended by the WHO ("WHO guidelines for the examination and processing of human ejaculate" Fifth edition 2010). According to this document, all spermatozoa are first of all graded as "normal / abnormal", and the latter, in turn, are divided according to the main location of the defect (pathology of the head, acrosome, neck, flagellum (tail). The reference value of the relative count of normal spermatozoa in the ejaculate, according to WHO guidelines, should be at least 50% [15].

The acrosome is located in the head of the spermatozoon, in front of the nucleus under the plasma membrane and plays an extremely important role in the process of fertilization. The acrosome is formed during spermatogenesis and can be considered as a modified lysosome. Acrosomal reaction - exocytosis of the counts of the acrosome for local destruction of the zona pellucida and overcoming this barrier by the spermatozoon (during the acrosomal reaction, the outer membrane of the acrosome and the cell membrane merge. In this case, hyaluronidases, proteases (including acrosin), glycosidases, lipases, neuraminidase, and phosphatases, which cleave molecules of the zona pellucida to overcome this biological barrier by the spermatozoon) [15]. Pathological changes in the acrosome were assessed based on WHO guidelines (the head should be smooth with a clear contour, oval. It should have a clearly defined acrosomal region occupying 40–70% of the head area. The acrosome should not contain large vacuoles and no more than two small vacuoles that should not occupy more than 20% of the head. The post acrosomal region should not contain any vacuoles) but without specifying the type of violation [15]. The results of the study were recorded as the total relative number of spermatozoa with acrosome pathology, which does not contradict the requirements of the above guidelines.

The pathology of the spermatozoa neck was carried out taking into account the WHO recommendations using the appropriate equipment, methodological and reagent base (the neck should be thin, clearly defined and approximately the same length as the head. The main axis of the neck should coincide with the central axis of the spermatozoon head. The cytoplasmic drop is examined as abnormal only if it is excessively large, that is, when it exceeds one-third the size of the sperm head. Neck and midsection defects: asymmetrical attachment of the midsection to the head (heteroaxiality), thick or irregularly contoured, excessively curved, abnormally thin or any combination of the above characteristics).

Pathological changes in the tail (flagellum) of the spermatozoon can be varied (defects in the main part of the flagellum: short, multiple, broken, hairpin, with a pronounced angle, width with an irregular contour, twisted, or any combination of these characteristics). However, in this study, the specific nature of violations of the morphology of cell organelles was not significant, since first of all, the task was to assess the effect of the studied drugs on spermatogenesis in general, according to generally accepted indicators of ejaculate. In this regard, all types of pathological changes in the tail were recorded as part of the isolation of one population of cells with a defect in this structure.

Actually, there are no clinical guidelines for male patients seeking fertility treatment. Meanwhile identifying the dietary factors that can influence male fertility potential is of high importance [16]. Several studies focus on antioxidant supplementation therapy [17,18]. No guideline exists for the antioxidant dose regimen and treatment duration as well.

The pharmacological activity of ZAG was revealed in the experimental models of oligo-, astheno- and teratozoospermia, which were characterized by statistically significant differences compared with the control groups [10].

The addition of the regulatory peptides of the prostate to this composition made it possible to develop Prostatilen AC medicine, which effectiveness has already been proven by real clinical practice studies in management of patients with chronic prostatitis and impaired fertility [11-14]. Zhukov et al. [13] demonstrated that the additional effect of ZAG increases the number of spermatozoa forms with progressive motility and their morphologically normal forms in semen analysis. In other study the treatment with Prostatilen AC for 20 days in patients with infertility more effectively improved semen parameters: progressive sperm motility, normal morphology compared to the group treated with Arginine-zinc complex [14]. At 5 days after the end of therapy, the proportion of spermatozoa forms with progressive motility increased by 62% compared to the baseline in the group of patients with chronic abacterial prostatitis who received Prostatilen AC ($p<0.001$) and only by 10% in the control group [14].

In our study the addition of ZAG to the regulatory peptides of the prostate composition in Prostatilen AC also resulted in significantly increased count of spermatozoa with a fast progressive motility (after therapy $p=0.0004$) and of normal forms of spermatozoa (after therapy $p=0.0118$) as well as in significantly decreased abnormal spermatozoa count with head, acrosome or neck pathology in the ejaculate compared to the reference drug.

Conclusion.

Prostatilen AC, rectal suppositories compared to the drug Prostatilen rectal suppositories, 3 mg, had a statistically significant and clinically significantly superior efficacy in relation to initially impaired sperm parameters (improve of sperm motility, restoration of morphologically normal sperm, decrease in forms of abnormal spermatozoa with head, acrosome or neck pathology). This drug could be recommended to use in the treatment of patients in whom chronic prostatitis occurs with concomitant disorders of sexual and reproductive functions.

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ВЛИЯНИЕ ДОБАВЛЕНИЯ АРГИНИЛ-ГЛИЦИНАТА ЦИНКА НА ПОВЫШЕНИЕ ЭФФЕКТИВНОСТИ БИОРЕГУЛЯТОРНЫХ ПЕПТИДОВ ПРЕДСТАТЕЛЬНОЙ ЖЕЛЕЗЫ ПРИ ЛЕЧЕНИИ ПАЦИЕНТОВ С НАРУШЕННЫМИ ПАРАМЕТРАМИ СПЕРМЫ.

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Резюме.

Препарат Простатилен®АЦ суппозитории ректальные был разработан на основе ранее зарегистрированного препарата, содержащего биорегуляторные пептиды простаты - Простатилен® суппозитории ректальные, 3 мг, и отличается введением в композицию активной фармацевтической субстанции цинка аргинил-глицината дигидрохлорид (ЦАГ). Целью исследования было оценить позитивный эффект добавления ЦАГ в состав препарата при лечении пациентов с нарушением сперматогенеза.

Обследовано 98 мужчин в возрасте 25-45 лет (в среднем 35,2±4,3 года) с верифицированным диагнозом хронического абактериального простатита и сопутствующими нарушениями репродуктивной функции в рандомизированном, мильтицентровом, открытом клиническом исследовании III фазы. Продолжительность участия пациентов в исследовании составила 14–16 дней, период скрининга – 2–3 дня, продолжительность терапии – 10 дней, итоговое обследование – 2–3 дня. Основная группа (n=49) получала терапию Простатилен АЦ 1 раз в сутки, контрольная группа (n=49) получала Простатилен 1 раз в сутки. Всем пациентам был проведен стандартный анализ спермограммы до и после лечения. Проводили анализ полученных данных.

В ходе анализа среднестатистических данных в группах сравнения было установлено, что исследуемый препарат Простатилен АЦ суппозитории ректальные приводит к увеличению общей популяции подвижных сперматозоидов (клетки А+В+С) на 14,3%, а препарат сравнения Простатилен суппозитории ректальные, 3 мг способствует повышению данного показателя на 4,1% по сравнению с результатами скринингового обследования с высокой эффективностью в отношении повышения относительного содержания сперматозоидов с быстрым поступательным движением (по окончании терапии Простатилен/Простатилен АЦ p=0,0004). Простатилен АЦ статистически значимо повышал содержание в эякуляте нормальных форм сперматозоидов, проявляя достоверно более высокую эффективность, чем Простатилен® (p=0,0118). У пациентов, получивших препарат Простатилен АЦ количество патологически измененных форм сперматозоидов уменьшилось на 12,4% (по окончании терапии - 55,57%), а в группе сравнения (Простатилен) на 6,5% (по окончании терапии - 58,90%) со статистически значимым уменьшением относительного содержания сперматозоидов с патологией головки, акросомы и шейки по сравнению с контрольной группой.

Простатилен АЦ по сравнению с препаратом Простатилен обладал статистически достоверно и клинически значимо превосходящей эффективностью в отношении исходно нарушенных показателей спермограммы (повышение содержания сперматозоидов с быстрым поступательным движением, восстановление популяции нормальных сперматозоидов, уменьшение относительного содержания сперматозоидов с патологией головки, акросомы и шейки). Данное лекарственное средство целесообразно использовать в терапии пациентов, у которых хронический простатит протекает с сопутствующими нарушениями половой и репродуктивной функций.

Ключевые слова: нарушение сперматогенеза, цинка аргинил-глицинат, биорегуляторные пептиды простаты, хронический простатит.