



B.U. Dzharbussynov Scientific Centre of Urology
under the Ministry of Public Health of the Republic of Kazakhstan
Kazakh Association of Urologists

НАУЧНЫЙ ЦЕНТР УРОЛОГИИ имени Академика Б.У. ДЖАРБУСЫНОВА

**Report on the Results of the Clinical Research
of SPERMOTREND Preparation
in Treatment of Chronic Abacterial Prostatitis
with Fertile Disfunction**

Almaty – 2012

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***REPORT
ON THE RESULTS OF THE CLINICAL
RESEARCH OF SPERMOTREND
PREPARATION
IN TREATMENT OF CHRONIC
ABACTERIAL PROSTATITIS WITH
FERTILE DYSFUNCTION***

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Actuality. Most specialists consider chronic prostatitis as an inflammatory disease with infectious genesis and possible addition of autoimmune disorders which are characterized by lesion of both parenchymatous and interstitial tissues of the prostate gland [Physicians' Desk Reference Online; Ebisch 1M et al., 2006; Scott R et al., 1998]. Prostate gland in men performs the exocrine secretory function and contains tissues which can have an endocrine response. The normal composition of the prostatic fluid is the main condition of fertility as the prostatic fluid ensures motion activity and viability of sperm cells outside the male body providing them with energy resources and protecting from unfavourable impact of the environment. It often happens that changes in the prostatic fluid cause disorders in ovum fertilization and development of prostatitis causes reproductive function disorders.

One of the main and frequently met complications in chronic prostatitis, irrespective of its form - bacterial or abacterial - is fertile dysfunction. Taking into account the high frequency of occurrence, complications and multi-vector nature of the disease we have decided to conduct a scientific and empirical research of the problem of prostatitis starting from anatomic-functional-morphological peculiarities of the prostate and consider the main existing diagnostic criteria and techniques, types of classifications and treatments, at that share accumulated scientific and empirical knowledge and modern approaches in the sphere of study and solution of the problem of prostatitis complicated by fertile dysfunction.

According to the epidemiological studies chronic prostatitis is quite common among young and middle-aged men and often complicated by copulative and generative functions. Most urologists of the world think that 20-43% of men suffer from chronic prostatitis, at that the quality of life of all patients significantly decreases [O.B. Loran and co-authors, 2002; O.I. Apolikhin and co-authors, 2004; V.N.Tkachuk, 2006; A.A. Kamalov and co-authors, 2006; A.A.Churakov, 2007; R. Alexandr, and co-authors, 1996; D. Shoskes and co-authors, 1999; I.Nickel, 2003 et al.]. In the opinion of G.W.

Druch and co-authors [1978], every second man suffers from this disease in a certain period of his life.

It was proved that microcirculation disorder in the prostate and deterioration of drainage of its acini play an important role in the pathogenesis of chronic prostatitis [V.N. Tkachuk and co-authors, 1989; V.V.Mikhailichenko, 1996; N.A.Lopatkin, 1998; P.V. Glybochko and co-authors, 2004; I. Nickel, 1999]. Blood circulation disorder in the prostate may be not only the basis for development of chronic prostatitis, but may provoke its relapses after treatment (V.N. Tkachuk, 2006). That is why in recent years some authors started to pay special attention to assessment of blood circulation in the prostate using a new method – Doppler sonography of the prostate – when examining patients suffering from chronic prostatitis – (A.I. Neymark and co-authors, 2000, 2004, 2007; Yu.G. Alyayev and co-authors, 2001, 2004, 2006; V.N. Tkachuk and co-authors, 2002, 2005, 2006; L.G. Spivak, 2005; Yu.M. Yesilevskiy and co-authors, 2006; M.F. Trapeznikova and co-authors, 2006, 2007; S. Veneziano and co-authors, 1995, M. Rifkin, 1997 et al.).

But available research reports are devoted mainly to differential and diagnostic value of this method of examination of patients with chronic prostatitis, and consideration of the problem itself is at the stage of accumulation of scientific data. Opportunities of Doppler sonography of the prostate have not been studied for selection of a method of treatment for patients with chronic prostatitis and prevention of complications after different methods of treatment of this disease. Very few specific data were published about the status of microcirculation of the prostate in the process of treatment of patients with chronic prostatitis using different preparations, and the status of blood circulation in the prostate was not studied on the long term basis after completion of treatment, especially there are no specific data concerning influence of preparations used in chronic prostatitis with fertile dysfunction. All this dictates the necessity to carry out a detailed research of clinical

effectiveness of preparations affecting spermatogenesis in chronic abacterial prostatitis.

Purpose: To study clinical and practical effectiveness of Spermotrend preparation in chronic abacterial prostatitis with fertile dysfunction.

Objectives:

- I. To evaluate influence of spermatogenesis stimulators on the sexual function.
- II. To analyze influence of Spermotrend preparation on spermatogenesis of patients with chronic abacterial prostatitis.

I. Influence of spermatogenesis stimulators on the sexual function.

The normal composition of the prostatic fluid is the main condition of fertility as the prostatic fluid ensures motion activity and viability of sperm cells outside the male body providing them with energy resources and protecting from unfavourable impact of the environment. It often happens that changes in the prostatic fluid cause disorders in ovum fertilization and development of prostatitis causes reproductive function disorders. Spermatogenesis is a complicated process ensuring quick increase of spermatogenesis, a long process of meiosis and numerous changes in spermatids in the course of their formation. Effect on reproductive cells may be caused during the reproductive period – mitotic division of spermatogenesis or during maturation of sperm cells; effect of the preparation on the mitosis and maturation of gonocytes was analyzed using qualitative cytological methods. After oral intake of 70-mg/kg of the body weight as a single daily dose of spermatogenesis stimulators during 20 days testicles of 8 rats were placed into the neutral formolcalcium and Serra solutions and after that placed into paraffin. Testicles of other 8 untreated animals were used for comparison (as reference). Histologic specimen from testicles were painted with hematoxylin (author - Mayer) and fast-green (author - Yordanov, 1976). Spermatogenesis, spermatocytes and spermatids of 40 divided cells were calculated for each animal both from the experimental and the reference groups through hypotonic tubes (total

quantity - 640), with the same diameter of tubes (determined by an ocular - micrometer) in stage VII, according to the classification by Leblond and Clermonn, 1952). Using the light microscope thickening of spermatogenetic cell layer was observed in divided cells of spermiducts and narrowing of their lumen in treated animals. It was detected from increase of the number of rows of sexual cells. The quantity of spermatogenes in 8 tested animals (i.e. in 32 sections of spermiducts) was equal to 58 spermatogenes on average in one spermiduct (between 48 and 63). The quantity of spermatogenes in one spermiduct in reference animals equalled to 38 (between 36 and 40 spermatogenes per duct). The average quantity of spermatocytes in spermiducts was identical to the number of spermatogenes. The quantity of spermatids in stage VII changed from 148 to 180 per spermiduct in tested animals (average value - 176). Their quantity in reference animals was between 112 and 125 (119 on average). The preparation significantly increased the number of spermatogenes, spermatocytes and spermatids in tested rats without any other effects on the diameter of spermiducts.

Influence on the DNA synthesis in gonocytes

Effect of the preparation of the DNA synthesis in sexual cells was analyzed using cytogistoradiography. Testicles of rats treated with spermatogenesis stimulator (7 days) and with 3H-thymidine (every second day) and later with colchicine (3 hours prior to decapitation) were placed into Serra solution and into paraffin.

Sections were covered with Ilford liquid emulsion and left for 25 days. Majority of 3 thymidine marked spermatogenes, types "A" and "B" were found in treated rats in comparison with reference animals. The average quantity of spermatogenes per section from spermiducts was equal to 5 (r in treated animals, 41 of them were marked by radioisotopes). These numbers were 5 and 18 accordingly in reference animals. Increase of the number of spermatogenes with 3H-thymidine in treated animals probably intensified the DNA synthesis under effect of the preparation as well as increase of the number of spermatogenes during the 5th stage of the cell cycle.

Influence on Leydig and Sertoli cells during testing

It is known that Leydig and Sertoli cells participate in the process of spermatogenesis. Qualitative cytological methods were used to assess the effect of the preparation on these cells. The results showed that the number of Sertoli cells increases in spermiducts when treated by spermatogenesis stimulator in comparison with reference animals.

The average number of Sertoli cells in a section of a spermiducts in treated animals was 29 against 19.5 (increase by 40%). Cytological research of the tests showed 110 differences in a number of Leydig cells between tested and reference animals.

Influence on concentration, mobility and viability of sperm cells

Mobility, concentration and viability of sperm cells in epididymis of rats treated during 30 days with the spermatogenesis stimulator, analyzed straight after decapitation. Sodium citrate was used as a dissolvent. The average number of sperm cells per ml was two millions higher in treated animals in comparison with the reference animals.

The quantity of moving sperm cells under the microscope was 8% higher in the treated animals. Besides, their sperm cells were more viable. Loss of movement improvement was observed in the 75th minute, on average. In the group of reference animals it was observed by the 45th minute.

Influence on libido

Effect of the spermatogenesis stimulator on the sexual behaviour was analyzed on the basis of male pigs with proved continuous sex impotence. The preparation was administered orally, and effect on the sexual behaviour and sexual reflexes was developed day by day. Individual animal reaction on the preparation was observed. Libido and sexual reflexes were restored in 71% of animals with total lack of libido: the animals were treated with a daily dose of 70 mg/kg during 10 days.

Animals with low libido and retarded sexual reflexes the restoration was observed in 100% of cases. Experimental data in relation to biological action of the spermatogenesis stimulator showed that its oral administration by rats significantly increased the number of spermatogenes, spermatocytes and spermatids without any changes in the diameter of spermiducts. This fact is connected with the proved stimulating effect on the spermatogenesis in general. It is known that the DNA synthesis takes place in the s-stage of the mitotic cycle. It is interesting to know that significant increase of A and B type spermatogenes was found in rats which were simultaneously treated by the spermatogenesis stimulator and 3H- thymidine during the s-stage.

Consequently a conclusion can be made that the preparation intensifies the mitotic activity of spermatogenes. Cytologically, expansion of Sertoli cells was observed which was caused by the preparation and one can assume that mitosis of these cells was also stimulated. An important role of Sertoli cells in regulation of spermatogenesis is well known (Kruzhevnoy 1967, Kerr and Klesier, 1974; Steinberger 1971), consequently, increase of the number of Sertoli cells in the process of treatment using the spermatogenesis stimulator should be connected with intensification of spermatogenesis. No changes were identified in Leydie cells of the tested animals which imply that action of the preparation on spermatogenesis probably does not include these cells. Literature data show that quick increase of spermatogenes in mammals and birds means FSH-stimulation (Stoinberger et al., 1964; Mlancini et al., 1966; Ishiis and Furua. 1975; Krueger etc., 1974). The authors suppose that influence of FSH on spermatogenesis takes place due to Sertoli cells. Radioimmunoassays of healthy men did not show any changes in the FSH-LEVEL after influence of the preparation for stimulation of spermatogenesis which assumes presence of the selective action of the preparation on gonocytes, on the other hand, raised LH-levels were found in healthy men in the process of stimulating treatment which assumes existence of the central action. Pharmacokinetic research showed absence of any measurable concentrations of the preparation in the plasma after oral administration by rats, but the chromatographic

method showed unidentified particles. The authors (Dikova and Ognyanova) suppose that biotransformation of the preparation takes place in the body. In such cases some of metabolites were formed during biotransformation, consequently, one can expect the effect of stimulation at the hypothalamic level.

The effect on libido of male pigs is obvious. The preparation not only stimulates libido, but possesses a therapeutic action also in cases of impotence reflected in the total absence of libido. Effect of the preparation on the quantity of sperm cells clearly shows that sperm cells of the treated animals are more viable and stable which implies better fertility. Many researchers think that sexual behaviour of animals and mobility of sperm cells depend on the levels of testosterone. Other authors think that sexual behaviour is modelled by dehydrotestosterone. The problem of the method of modelling sexual behaviour is still disputable. If we assume that androgenic-like factors were formed through biotransformation in the body then they would not stimulate changes in interstitial cells.

Special attention must be drawn to harmlessness of the preparation. No evidence of acute, subacute and chronic toxicity was found in the course of experimental behavioural, haematological, functional, biochemical and morphological studies. No data concerning carcinogenic and teratogenic effects are proved.

The fact that the preparation has an effect on the hormone balance in the body without disordering regulating mechanisms is also very important.

Combined action of the preparation лекарства (ability to stimulate sexual libido and spermatogenesis) and absence of unfavourable actions characterize it as the main method of treatment for men with sexual dysfunction, especially in case of chronic prostatitis.

Preparations for stimulation of spermatogenesis restore and improve libido in all forms of chronic prostatitis after administration of the average daily dose of

1.5 g during the period of 30-40 days. It implies that not only reduced libido is stimulated but there is a therapeutical effect in chronic prostatitis complicated by fertile dysfunction. The assumption that the preparation has a favourable effect on mobility of sperm cells after 60 days of administration correspond to the experimental data according to which it stimulates both mitosis and maturation of embryonic cells.

It is known that at least 80 days passes from the beginning of division of spermatogenes till formation of mature sperm cell in men, consequently, concentration of sperm cells in sperm are different within this period. Patients who use spermatogenesis stimulators during 90 days have very good results in terms of mobility and concentration of sperm cells in the ejaculate. Research of the ejaculate in patients treated during 60 days proved the evident effect on the mobility of sperm cells and insignificant effect on their concentration based on identical initial levels of sperm cells in patients in nosologic groups before treatment. It proves the fact that the minimum therapeutic cycle must be as long as one embryonic cycle (i.e. 80-90 days in men).

II. Analysis of influence of Spermotrend preparation on spermatogenesis in patients with chronic abacterial prostatitis.

Materials and methods of research:

Patients undergoing hospital treatment with subsequent outpatients observation aged 18 to 50 (average age 29.5 ± 5.1 years) with diagnosed “Chronic abacterial prostatitis with fertile dysfunction” in the department “Andrology” of the Scientific Center of Urology named after B.U. Dzharbusynov. Duration of research and clinical observation was 90 days, duration of research – from 15.06 till the 15th of September 2012.

Study design and inclusion/exclusion criteria:

Inclusion criteria: males from 18 to 50 with the diagnosis of **chronic abacterial prostatitis with fertile dysfunction**.

Exclusion criteria:

- 1) Patients with CBP (chronic bacterial prostatitis) accompanied by BPH (benign prostatic hypertrophy);
- 2) Alcohol abuse;
- 3) Diabetes mellitus;
- 4) Cardiovascular diseases and other somatic pathology.

Main group, 25 patients

General requirements:

1. Observance of the protocol of bioethical agreement.
2. Observance of the research conditions (refusal from alcohol, information about any side effects of the preparation, administration of the preparation according to the prescribed scheme).

Control group, 25 patients

General requirements:

1. Observance of the protocol of bioethical agreement.
3. Observance of the research conditions (refusal from alcohol, information about any side effects of the preparation, administration of the preparation according to the prescribed scheme).

Research methods:

Results of the methods before treatment:

1. IIEF questionnaire
2. Testosterone
3. Immunogram
4. MAR-test
5. Spermogram

Results of the methods after treatment:

1. IIEF questionnaire
2. Testosterone

3. Immunogram
4. MAR-test
5. Spermogram

Synergism of antioxidants containing in SPERMOTREND® ensures maximum natural revitalization of sperm cells. SPERMOTREND® increases the volume of ejaculate. SPERMOTREND® increases concentration and mobility of sperm cells. SPERMOTREND® intensifies libido and satisfaction. SPERMOTREND® stimulates diuresis and does not cause side effects, improves sexual desire and satisfaction.

The most important components of SPERMOTREND® are:

Fructose – the main source of carbohydrates of the spermatic fluid which provides more than a half of the quantity of carbohydrates consumed by sperm cells and is irreplaceable in ensuring mobility of sperm cells. (3)

Zinc (in the form of zinc sulfate) – an irreplaceable mineral playing an important role in ensuring mobility of sperm cells and achievement of optimal concentration of testosterone. The amount of zinc is usually reduced in case of chronic vesiculitis of prostate gland. (4)

Vitamin B6 – participates in many biochemical reactions which are connected with metabolism of amino acids and carbohydrates, synthesis of nucleic acids and other processes. This vitamin helps increase the level of ABL-cholesterol and stabilize blood pressure. (5)

Vitamin B12 – the vitamin with the most complex structure. It is known that Vitamin B12 ensures many processes the most important of which are DNA and RNA synthesis, integrity of the nervous system, biosynthesis of fatty acids. Besides, Vitamin B12 plays a role of an activator in energy processes.

Folic acid in combination with vitamin B12 participates in DNA, RNA and protein synthesis and has a prophylactic effect in case of deficiencies of the neurological character. Preparations containing folic acid significantly increase concentration of sperm cells in subfertile men. (6)

Selenium – an effective antioxidant. Selenium is found in GSHPx-4 which influences sperm cells as an antioxidant and ensures their regular structure. Administration of selenium-containing preparations by subfertile men will help increase the mobility of sperm cells and their successful fertilization. (7)

Pygeum africanum (pygeum palm bark extract) – its high effectiveness in treatment of benign prostatic hypertrophy and relief of symptoms connected with it, such as frequent uriesthesia at night, is proved; it also improves the residual volume and peak flow of urine. (8)

Arginine – nitrogen monoxide precursor, a natural vein-expanding substance for which positive effect on the erectile dysfunction is typical.

Vitamin E – a strong antioxidant which improves spermatogenesis.

Packing: a bottle containing 90 capsules.

Application:

Take 1 capsule twice a day.

Ingredients:

Pygeum Africanum;

Zinc sulfate;

Sodium selenite;

Pyridoxine (vitamin B6);

Ascorbic acid (vitamin C);

Folic acid; cyanocobalamin (vitamin B12);

DL-alpha- tocopherol (vitamin E);

Arginine;

Carnitine;

Fructose;

Microcrystalline cellulose.

Results of the research of 50 males 18 to 50 years old (average age 29.5 ± 5.1 years old) form the basis of the research. Period of the disease varies from 4 months to 9 years (2.9 years on average), the diagnosis of chronic abacterial prostatitis was confirmed by the data of clinical, laboratory, ultrasonic studies and

Doppler sonography. Along with the basic therapy (anti-inflammatory treatment, local treatment in the form of rectal suppositories, alpha-adrenoreceptor blocking agents, vitamin therapy and physiotherapy), the main group took Spermotrend according to the following scheme: 1 capsule twice a day. Along with the basic therapy, the treatment scheme of the control group included tocopherol acetate (vitamin E) 1 capsule twice a day instead of Spermotrend (placebo effect) which was taken during 90 days. Results of the research for the both groups are given below.

Table 1 – Results of the main indicators.

Research methods	Results prior to treatment		Results after treatment (90 days)	
	Control group (n=25)	Main group (n=25)	Control group (n=25)	Main group (n=25)
IIEF questionnaire	17.9±2.9	13.2±1.3	17.9±2.1	18.2±2.1
Testosterone mME/ml	7.6±1.3	7.9±1.2	8.6±1.5	10.7±2.5
Immunogram % T-lymphocytes %	58±2.3	59±1.9	61±1.7	65±2.2
B- lymphocytes %	12±1.7	13.2±1.9	14±2.2	16±2.7
MAR-test % (IgA-IgG)	52±3.2	53±2.9	55±2.7	62±3.8
Spermogram Ejaculate mobility (%) class A+B	37.3±4.2	38.2±3.2	47±3.7	56±4.3
Ejaculate volume (p < 0.01)	3.3 ± 0.5 ml	3.1±0.3 ml	3.7 ± 0.9 ml	4.8±0.2 ml
Ejaculate viscosity (p < 0.05)	18.0 ± 2.5	17.8±2.7 mm	16.2 ± 1.2 mm	14.3±1.1 mm
Ejaculate dilution period (p < 0.01)	25.9 ± 4.5 min	24.8±3.2 min	21.2 ± 4.0 min	15.7±2.9 min
Level of citric acid in ejaculate (p < 0.05)	17.5 ± 1.9 mmol/l	16.9±1.7 mmol/l	18,8 ± 2.1 mmol/l	24.8±1.9 mmol/l

When analyzing the IIEF scale, the total score in the majority of patients of the main group after treatment mostly increased due to question 5: “How often were you satisfied in attempts to have a sexual intercourse?” Before treatment 17 (68%) patients of the main group replied – “very seldom, less than in the half of cases”, after treatment 22 (88%) patients replied – “often, much more than in the half of cases”.

Results of the testosterone level study in both groups prior to treatment were low, dynamics is observed in the main group after treatment, testosterone increased by more than 27% which demonstrates positive effect of Spermotrend on production of gonads. The immunogram conclusion reliably shows that continuous administration of the spermatogenesis stimulator has a modelling effect on the condition of T- and B- systems of the immunity, by more than 10% in the main group. At the same time, it should be noted that in our opinion prescription of a special immune-correcting treatment must be taken with special care and used only in cases of detection of pathologic shifts evident based on the results of the immunological study. D.Yu. Pushkar and A.S. Segal (2003) hold the same opinion.

The improvement of indices of antisperm antibodies in the main group by 16% on average and higher proves that spermatogenesis stimulators, Spermotrend in this case, have a positive effect on the ratio (percentage) of normal actively moving sperm cells, but covered by antisperm antibodies, to the total quantity of sperm cells with the same characteristics.

Before using Spermotrend, 12 (48%) of 25 patients with chronic abacterial prostatitis demonstrated disorder in mobility of sperm cells in the ejaculate whereas after treatment this symptom was diagnosed only in 6 (24%) cases which is 2 times less. After treatment the volume of ejaculate in patients increased from 3.1 ± 0.3 ml to 4.8 ± 0.2 ml ($p < 0,01$), the ejaculate viscosity decreased from 17.8 ± 2.7 mm to 14.3 ± 1.1 mm ($p < 0,05$), the ejaculate dilution period reduced from $24.8 \pm 3,2$ min to 15.7 ± 2.9 min ($p < 0,01$), but what is mostly important the level of citric acid in the ejaculate increased from 16.9 ± 1.7 mM/l to 24.8 ± 1.9 mM/l

($p < 0,05$) which witnesses the improvement of the prostate function in patients with chronic abacterial prostatitis after treatment using Spermotrend.

Conclusion

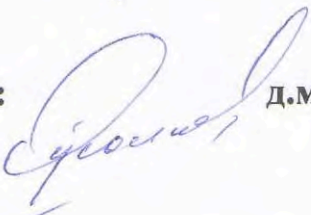
- Spermotrend is a fundamentally new pathogenetic preparation to treat chronic abacterial prostatitis with fertile dysfunction.
- The conducted clinical study has shown the high effectiveness and safety of Spermotrend when treating patients suffering from chronic abacterial prostatitis.
- Treatment using this preparation during 90 days in a dose of 1 capsule twice a day caused significant improvement not only in the fertile function but notable improvement of the quality of life of the patients, helped stabilize blood circulation in the prostate and reduce or eliminate swelling of this organ, increased mobility of sperm cells in the ejaculate and improved the sexual function of patients with chronic abacterial prostatitis.
- Clinical effect of administration of Spermotrend demonstrated positive influence on the status of the cell- and antibody-mediated immunity and reliable influence on the ratio of antisperm antibodies.
- But we think that duration of treatment of patients with chronic abacterial prostatitis must not be less than 90 and not 30 days as it is usually specified in treatment standards and protocols, especially in case of fertile dysfunction.

Research Director

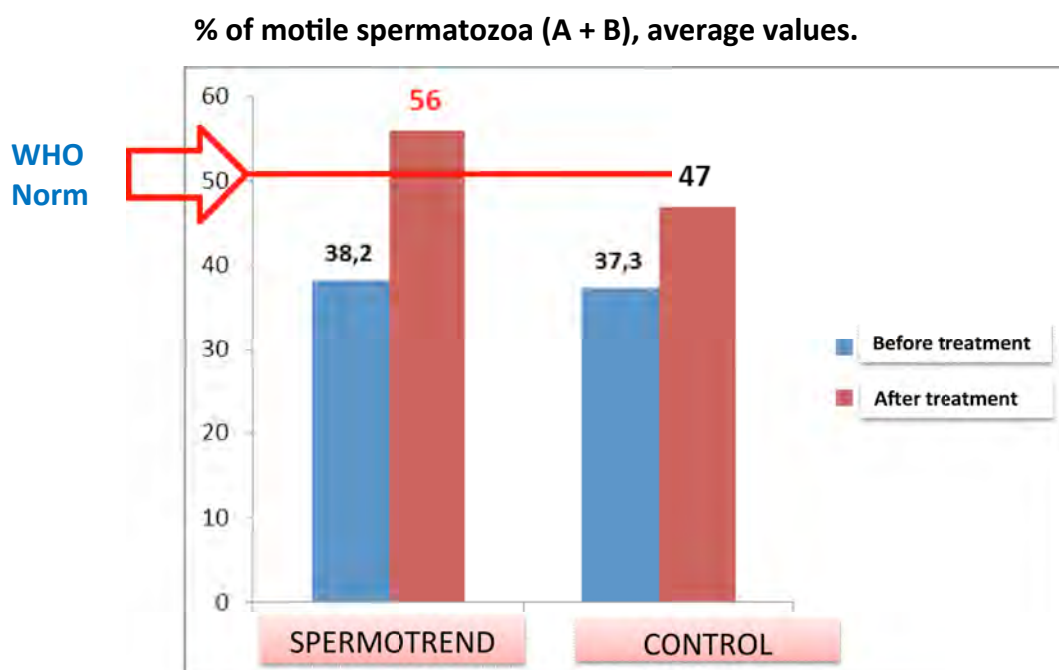
M.D., prof. M.K. Alchinbayev

Research Supervisor

M.D., prof. T.E. Hussainov

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Научный руководитель:  **д.м.н. проф. Хусайнов Т.Э.**

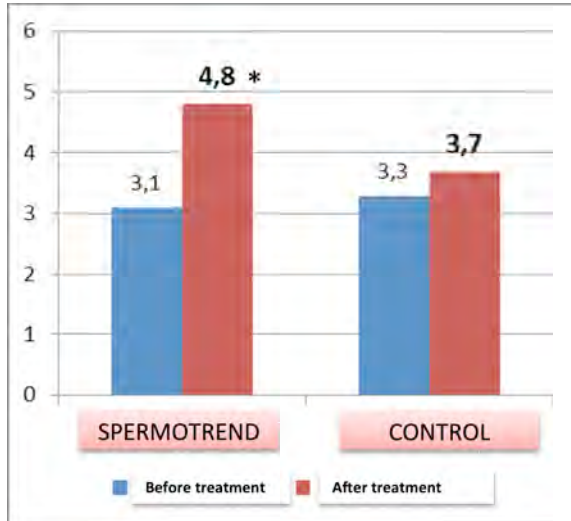
Spermotrend - restores sperm motility to normal levels



WHO norm 2009 – the content of at least 50% of motile spermatozoa

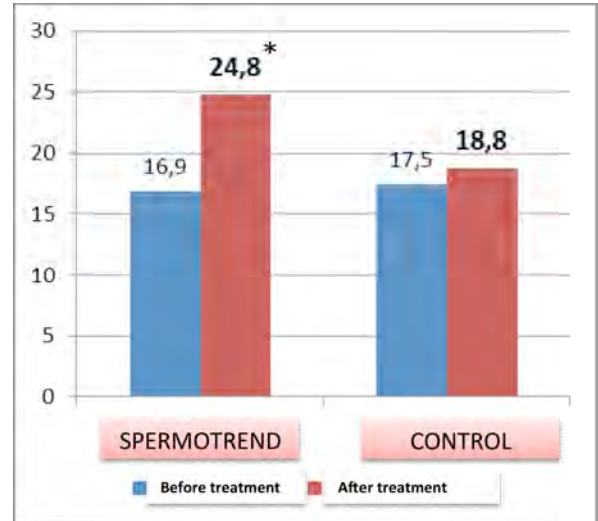
Spermotrend – improves ejaculate parameters and prostate function

Increases volume, ml



* $p < 0,01$

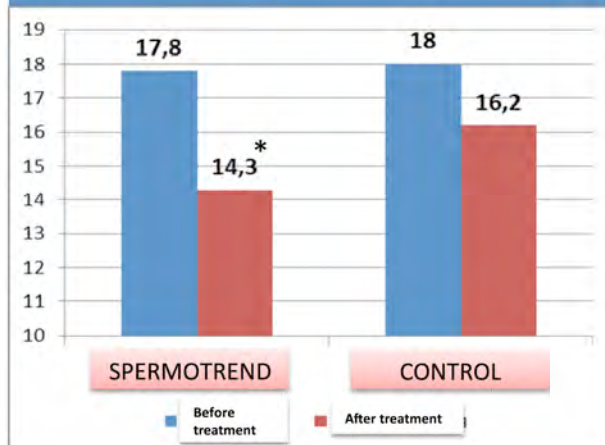
Increases citric acid content, mmol/



* $p < 0,05$

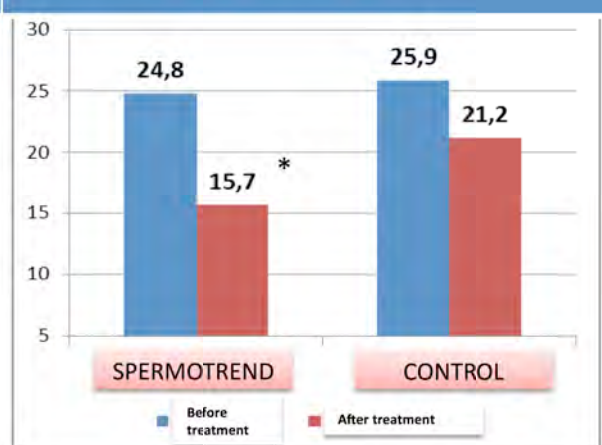
Spermotrend – improves ejaculate parameters

Reduces viscosity, mm

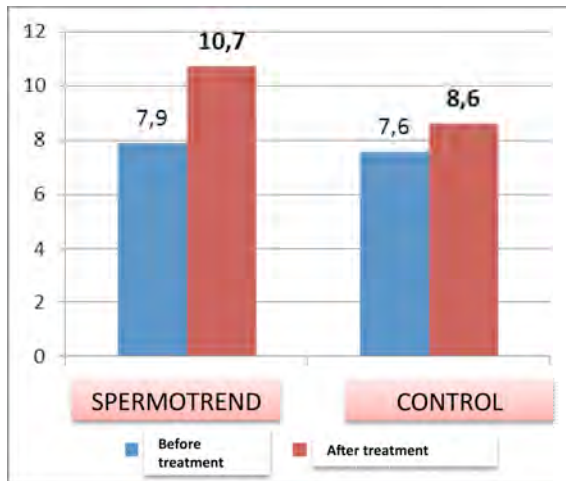


$p < 0,05$

Accelerates liquefaction time, min.



$p < 0,01$



Spermotrend
increases testosterone
levels by 27%

How did patients who received Spermotrend answer the question: "When trying to have sexual intercourse, how often were you satisfied?"

- ❖ Before treatment - 68% - "occasionally, less often than half the time"
- ❖ At the end of treatment, 88% – "often, much more often than in half of cases."