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Research Article

The Influence of the Combined Use of Various Forms of Preparations Containing Oxidized Dextran on the Reproductive Status of Men with Idiopathic and Secondary Infertility

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Abstract

Introduction: The study of fertility is of great scientific interest due to the impact of numerous external factors on the body, which significantly affect male reproductive status. The assessment of changes in spermograms is necessary for the diagnosis, treatment, and prognosis of recovery in various forms of infertility. The results of this study are based on the dynamic examination of ejaculate parameters using the active substance - oxidized dextran, in the form of capsules for oral use and rectal suppositories.

The Aim of the Study: to evaluate the effectiveness of using a combination of rectal and oral forms of oxidized dextran in the treatment of men with idiopathic and secondary infertility.

Materials and Methods. At the base of LLC "RMDC Clinic," 37 patients aged 18 to 55 were examined, of whom 65% were found to have idiopathic infertility, while the rest had secondary infertility as a complication of the latent course of chronic nonspecific prostatitis.

The evaluation of the main clinical and laboratory indicators was conducted: assessment of the basic spermogram, MAR-test with determination of IgA and IgG fractions (%) and the sperm DNA fragmentation index (SDFI). All patients were offered a new method for correcting pathospermia with a total duration of 4 months, during which for the first month, men received oxidized dextran in the form of rectal suppositories "ANDROEXPERT SV1" (active ingredient content, oxidized dextran - 100 mg per suppository) every night. In the following 3 months, the intake of rectal suppositories continued in the same dosage with a frequency of "every other day"; additionally, patients received the same medication in the form of capsules (active ingredient content, oxidized dextran - 0.25 mg per capsule) twice daily.

Results: The concentration of spermatozoa by the end of the treatment course increased compared to the baseline values by 73.1% ($p < 0.001$), the total number of spermatozoa in the ejaculate increased by 63.6% ($p < 0.001$); the fraction of progressively motile spermatozoa ("A" + "B") increased by 90.5% ($p < 0.001$) due to the "A" fraction, which increased tenfold ($p < 0.025$), which affected the increase in total sperm motility ("A" + "B" + "C") by 28.9% ($p < 0.001$), the fraction of immotile spermatozoa ("D") decreased by 23.6% ($p < 0.001$). The sperm viability rate increased by 20% ($p < 0.001$). A positive trend was observed in the MAR-test indicators,

accompanied by a radical decrease in the values of the IgG-dependent fraction of ASAT by 85.7% ($p < 0.019$), as well as a decrease in the FDNK index by 43.9% ($p < 0.001$).

Conclusion: As a result of the clinical trial of the method we proposed for correcting idiopathic and secondary male infertility using a combination of two forms of oxidized dextran administration – rectal suppositories "ANDROEXPERT SV1" and capsules "ANDROEXPERT" for oral use – an improvement in the main spermological parameters was noted, as well as an increase in the immunological and genetic status of the ejaculate.

Keywords: Oxidized Dextran; "ANDROEXPERT" Capsules and Suppositories; Male Infertility; Ejaculate; Spermogram

Introduction

Currently, the study of male infertility appears to be relevant, as it has become widespread in the context of modern urbanized society. Deterioration of reproductive function in men is diagnosed, according to various researchers, in 5 to 15% of the entire male population and in 40 to 60% of men with infertility in couples [1-3].

Most often, male infertility is classified as idiopathic when the cause of fertility impairment is not identified, but sperm quality deteriorates, usually uniformly across all major parameters of sperm analysis. In fact, the cause of such changes is multifactorial [1-6]. These are physical inactivity, obesity, emotional and oxidative stress, arterial hypertension, chemical and physical factors, including electromagnetic radiation from household appliances and electronic devices. Undoubtedly, both urological and somatic pathology contribute to male infertility. The main cause of secondary infertility is chronic prostatitis [2,7-13]. Often, the conclusion of the spermogram indicates: oligoasthenoteratozoospermia (OAT syndrome). In this situation, the onset of pregnancy is usually extremely doubtful even with fully preserved reproductive function in the woman [1-4]. Often, when the secretory function of the male reproductive glands is impaired, sexual function disorders also arise, which negatively affect the man's reproductive status [10].

Under the influence of the aforementioned factors, venous stasis develops in the pelvis [8-11], leading to a whole range of metabolic disorders not only in the prostate but also in other reproductive glands: seminal vesicles, testes, and epididymis, which results in their dysfunction. In conditions of prolonged and persistent vascular spasm under the influence of chronic oxidative stress, tissue hypoxia develops, which is exacerbated by dysfunction of lymphatic and blood circulation [4-11,14].

The treatment of idiopathic and secondary infertility, therefore, presents enormous difficulties due to the fact that correcting this condition often requires not only eliminating a number of causes that led to it but also improving the structural and functional organization of the gonads, which have been under the influence of negative factors for an extended period [8-13]. Medication therapy—antibiotics, anti-inflammatory drugs, agents that improve tissue metabolism, prostate-protective agents, as well as vitamin-mineral complexes—especially in monotherapy, are ineffective due to the persistent vascular spasm of the target organ, which is under the influence of oxidative stress in a state of venous stasis, circulatory disorders, ischemia, and tissue hypoxia [8,10,11,13,14]. Therefore, at present, prolonged courses of comprehensive drug therapy are used, in combination with courses of physiotherapy [1,4,10,13].

There are many methods of local rectal administration that facilitate the delivery of the active substance to the prostate tissue in cases of inflammatory or circulatory disorders in the pelvic area [8-11]. The simplest and most accessible form in this case is rectal suppositories, which have recently gained widespread use [2,3,7,8,10]. Earlier, we demonstrated the effectiveness of using oxidized dextran in the form of rectal suppositories in the treatment of patients with chronic prostatitis (CP) [2,3,7,10].

This study presents data on the clinical trial of the combined (local and oral) use of oxidized dextran as an active substance in the treatment of idiopathic and secondary male infertility. Oxidized dextran (OD) was used in the form of rectal suppositories "ANDROEXPERT SV1": oxidized dextran 100 mg, excipients: rutin 50 mg, EDTA 50 mg, cocoa butter 2.34 g. Composition

of "ANDROEXPERT" capsules for oral use: active ingredient, oxidized dextran 25 mg, excipients: barberry fruit extract 12.5 mg, microcrystalline cellulose 292.5 mg. The method for obtaining oxidized dextran was developed at the Federal Research Center for Fundamental and Translational Medicine (Novosibirsk, Russia). The drug has undergone preclinical safety studies according to GLP standards [15-17]. OD is a linear polysaccharide with an average molecular weight of 40 kDa. Its distinguishing feature is that part of the glucose rings are opened, and the number of carbonyl groups is significantly higher than in its non-oxidized form. In terms of pharmacological activity, it is similar to β-1,3-glucans. Due to its conformation, OD is capable of selectively receptor-mediated activation of tissue macrophages, which release a wide range of anti-inflammatory cytokines and tissue proteases into the extracellular environment, actively eliminating manifestations of inflammation and hypoxia in the tissues. The effects of OD have been experimentally and clinically confirmed: anti-inflammatory, lytic, antifibrotic, and thrombolytic [2,3,7,10,15-17].

The Aim of the Study

To evaluate the effectiveness of using a combination of rectal and oral forms of oxidized dextran in the treatment of men with idiopathic and secondary infertility.

Materials and Methods

The study was conducted at the LLC "RMDC Clinic" (Novosibirsk, Russia). Thirty-seven patients with idiopathic secondary infertility aged 18 to 55 were examined; among them, 65% (24 individuals) were diagnosed with idiopathic infertility; 35% (13 individuals) were found to have secondary infertility as a complication of latent chronic nonspecific prostatitis; in two patients, due to a positive MAR test, an autoimmune factor could not be excluded. All conducted studies were performed with the informed consent of the patients and in accordance with the ethical norms of the Helsinki Declaration (WMA, Edinburgh, Scotland, 2000), taking into account the explanatory note of paragraph 29, approved by the General Assembly of the WMA (Washington, 2002). The patients were examined according to the standard protocol, including information on the collection of complaints, medical history, general examination, and physical methods. All patients were assessed for sperm parameters at the beginning and end of the treatment course according to our proposed method, in accordance with the WHO laboratory manual for the examination and processing of human semen (6th edition) [18-20]. In addition to basic semen analyses, sperm viability (by Bloom, %), MAR-test (IgA and IgG, %), which determines the percentage of active sperm covered with anti-sperm antibodies (ASAT) to sperm free from ASAT, and the index of fragmented DNA (FDNA) in sperm [19-21] (see Table 1) were evaluated.

All examined men were combined into a group. The observation period lasted 4 months: for one month, patients received the active substance, oxidized dextran, in the form of rectal suppositories "ANDROEXPERT SV1" (1 suppository with a dose of 100 mg of the active substance, oxidized dextran) daily (once a day, at night), and for the following 3 months, the intake was continued with a frequency of "every other day." Additionally, during these three months, patients received the oral form of OD in the form of "ANDROEXPERT" capsules with an active substance dosage of 25 mg per capsule. The daily dose of the active substance, oxidized dextran for this form, was 100 mg: 2 capsules twice a day.

Statistical analysis of the study results was conducted using the statistical software package "STATISTICA v. 10.0" (Stat Soft Incorporated, USA). To assess the type of distribution of the studied variables, the Shapiro-Wilk W test was used. Since most of the values had a non-normal distribution, median (Me), lower (Q1), and upper (Q3) quartiles were used for descriptive statistics. To analyze the changes in values after treatment, the non-parametric Wilcoxon Matched Pairs Test was applied. Statistically significant differences were considered at $p < 0.05$, where p is the probability of a Type I error when testing the null hypothesis [22,23].

Results

By the end of the treatment course, the examined patients showed positive changes in all spermogram parameters: sperm concentration (million/ml), total sperm count in the ejaculate (million), fraction of progressively motile sperm (A - rapidly motile, B - slowly motile, %), total sperm motility (A+B+C, %), fraction of immotile sperm (D, %), and sperm viability (%). Moreover, a decrease in the values of the MAR-test indicators (mainly due to IgG) and sperm DNA fragmentation (Table 1) was noted.

Thus, the concentration of seminal fluid with a high degree of significance at the end of the treatment course significantly

increased by 73.1% ($p < 0.001$; Table 1). In this context, it was logical that the total number of sperm in the ejaculate increased by 63.6% ($p < 0.001$); the fraction of progressively motile sperm ("A" + "B") increased by 90.5% ($p < 0.001$), mainly due to rapidly motile sperm (fraction "A"), which increased tenfold ($p < 0.025$; Table 1). Such data logically influenced the improvement of the overall sperm motility indicator ("A" + "B" + "C") by 28.9% ($p < 0.001$); at the same time, the indicator of the immotile sperm fraction ("D") decreased by 23% ($p < 0.001$). The viability of spermatozoa increased by 20% ($p < 0.001$).

Earlier, at one stage of our research on the properties of OD, it was shown that, alongside its anti-inflammatory, litholytic, and defibrinolytic effects, a gonadotropin-like effect was observed in the treatment of patients with chronic prostatitis associated with secondary infertility [2,3]. The present study using OD as a factor for correcting pathospermia demonstrates not only a positive dynamics in the most significant spermological parameters of infertile men but also its ability to compensate for the immune and genetic status of the ejaculate. This can be concluded from the positive dynamics of the MAR-test indicators, accompanied by a radical decrease in the values of the IgG-dependent fraction of ASAT (by 85.7%; $p < 0.019$) and the FDNK indicator (by 43.9%; $p < 0.001$; Table 1) by the end of the treatment course.

Indicator, units of measurement	**The value of indicators before correction, Me [QL; Qh]; n = 37**	**The value of indicators after correction, Me [QL; Qh]; n = 37**	**Statistical Value of Differences, "p" (Wilcoxon Matched Pairs Test)**
Ejaculate volume, ml	3,0 [2,6; 4,0]	4,0 [2,5; 4,4]	0,696
Viscosity, cm	1,0 [0,5; 1,5]	1,0 [0,5; 1,8]	0,745
Liquefaction time, min.	30,0 [30,0; 0,0]	30,0 [30,0; 30,0]	0,115
Sperm concentration, million/ml	26,0 [9,0; 44,0]	45,0 [22,0; 62,0]	<0,001*
Total number of sperm in the ejaculate, million	81,0 [32,0; 140,0]	132,5 [70,0; 211,5]	0,001*
Motile sperm fraction («PR»: «A» +«B»), %	21,0 [12,0; 39,0]	40,0 [25,0; 57,0]	<0,001*
Fraction of rapidly motile spermatozoa («A»), %	2,5 0,0; 16,0]	25,0 [9,2; 33,0]	0,025*
Fraction of slowly motile spermatozoa («B»), %	11,8 [5,0; 21,0]	21,9 [14,0; 27,0]	0,056
Total sperm motility («A»+«B»+«C»), %	45,0 [30,0; 61,0]	58,0 [45,0; 71,0]	<0,001*
Fraction of non-motile spermatozoa («D»), %	55,0 [39,0; 70,0]	42,0 [29,0; 55,0]	<0,001*
Agglutination (severity of, в «+»)	0,0 [0,0; 0,0]	0,0 [0,0; 0,0]	0,686
Leukocytes, million/ml	0,4 [0,1; 0,8]	0,3 [0,1; 0,5]	0,059
Cells of spermatogenesis, million/ml	0,6 [0,2; 2,0]	1 [0,3; 2,0]	0,607
Kruger morphology, million/ml	2,0 [1,0; 3,0]	2,0 [1,0; 5,0]	0,216

Viabilityъ, %	60,0 [49; 70]	72,0 [65; 80]	<0,001*
Mar-test IgA, %	3,0 [0; 10]	0,5 [0; 10,5]	0,106
Mar-test IgG, %	3,5 [0; 10]	0,5 [0; 7,5]	0,019*
Fragmented sperm DNA, %	23,0 [17; 35]	12,9 [9,2; 18]	<0,001*

Table 1: The dynamics of spermological indicators in the studied patients diagnosed with infertility by the end of the treatment course using a combination of various forms of "ANDROEXPERT" drugs.

Note: "*" - The difference in indicators "before" and "after" treatment is significant: - $p < 0.05$.

The observed positive therapeutic effect can be explained by the increased bioavailability of the active substance to the target organs (testes, epididymis, prostate) when using a combined method (rectal and oral administration). We associate this therapeutic effect with the lymphotropic properties of oxidized dextran and its ability to selectively, receptor-mediated activate macrophages. At the same time, the activating effect extends to both the tissue population of macrophages and the population of macrophages circulating in the systemic bloodstream and lymph. From the perspective of pathophysiological mechanisms for correcting spermatogenesis disorders, we propose using oxidized dextran as an activator of testicular macrophages and a means to modulate the phenotype of tissue macrophages and cytokine expression depending on their microenvironment. Such a pathophysiological mechanism of the therapeutic efficacy of oxidized dextran has been previously described by us in an integrated assessment of data from experimental-clinical studies [24].

Thus, the results of our clinical trial of the combined course using oxidized dextran in the form of rectal suppositories "ANDROEXPERT SV1" and capsules "ANDROEXPERT" indicate a significant improvement in the reproductive status of men diagnosed with idiopathic and secondary infertility against the background of chronic prostatitis, as well as an increase in the likelihood of conception and the birth of a healthy child in the couple.

Conclusion

Thanks to the clinical method we proposed for correcting idiopathic and secondary male infertility using a combination of various forms of oxidized dextran administration (rectal suppositories "ANDROEXPERT SV1" and capsules "ANDROEXPERT" for oral use), it is possible to effectively correct spermological parameters and restore reproductive function. The therapeutic efficacy of oxidized dextran appears to us to be pathophysiologically justified in terms of receptor-mediated activation of all macrophage populations and modulation of their phenotype to optimize the correction of spermatogenesis disorders. The therapeutic effect of oxidized dextran is accompanied by an increase in sperm concentration, their total count in the ejaculate, fractions of progressive motility of sperm, their overall motility with a simultaneous decrease in immobile forms, an increase in their viability, as well as positive dynamics in the results of the MAR-test and DNA fragmentation of sperm, which indicates an improvement in the immunological and genetic status of the ejaculate, and overall, an enhancement in male fertility.

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