https://doi.org/10.17816/uroved41756

OUR EXPERIENCE OF APPLICATION OF LOW-LEVEL LASER THERAPY IN RED SPECTRUM IN MALE IDIOPATHIC SECRETORY INFERTILITY

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For citation: Potapova MK, Borovets SYu, Slesarevskaja MN, Al-Shukri SKh. Our experience of application of low-level laser therapy in red spectrum in male idiopathic secretory infertility. *Urology reports (St. Petersburg)*. 2020;10(3):209-216. https://doi.org/10.17816/uroved41756

Received: 27.07.2020 Revised: 18.08.2020 Accepted: 23.09.2020

Introduction. Due to insufficient efficacy of medical therapy of idiopathic secretory male infertility there is a need to develop and apply more resultative methods of treatment.

The aim of our study was to assess the efficacy of low-level laser therapy (LLLT) in red spectrum on sperm parameters, sperm DNA fragmentation (SDNAF) and MAR-test rate in men with idiopathic infertility.

Patients and methods. 85 men with idiopathic infertility were examined, 50 of them (first group) were treated with LLLT and 35 (second group) didn't have course of LLLT. Average age of patients of the first and second groups was 31.4 ± 1.3 and 32.3 ± 1.4 years. LLLT was performed in red spectrum on a Rubin-C device (Russia). 10 laser therapy procedures were carried out every two days with active luminescence for 10 minutes of both testicles. Male hormone panel, semen analysis, MAR-test, SDNAF were assessed before and after the treatment.

Results. LLLT in patients of the first group resulted in significant increase in ejaculate volume, sperm viability, number of morphologically normal sperm forms (by an average of 11, 9 and 23% respectively), and active mobile sperm forms by an average of 14 and 19% one and two months after the therapy respectively. In 12 patients of the first group with initially increased SDNAF its level became normal after the treatment. Significant decrease of MAR-test we searched out in patients of the first group with its initial level less than 30%. As a result of the treatment, pregnancies developed in 10 (20%) out of 50 couples in the first group.

Conclusions. LLLT in red spectrum leads to significant improvement of sperm quality in patients with idiopathic infertility, normalizes sperm DNA-fragmentation level and decreases MAR-test level.

Keywords: male infertility; low-level laser therapy; red spectrum.

НАШ ОПЫТ ПРИМЕНЕНИЯ НИЗКОИНТЕНСИВНОЙ ЛАЗЕРНОЙ ТЕРАПИИ В КРАСНОМ СПЕКТРЕ ПРИ ИДИОПАТИЧЕСКОМ СЕКРЕТОРНОМ БЕСПЛОДИИ У МУЖЧИН

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Для цитирования: Потапова М.К., Боровец С.Ю., Слесаревская М.Н., Аль-Шукри С.Х. Наш опыт применения низкоинтенсивной лазерной терапии в красном спектре при идиопатическом секреторном бесплодии у мужчин // Урологические ведомости. – 2020. – Т. 10. – № 3. – С. 209–216. https://doi.org/10.17816/uroved41756

Поступила: 27.07.2020 Одобрена: 18.08.2020 Принята к печати: 23.09.2020

Введение. В связи с недостаточной эффективностью медикаментозной терапии идиопатического секреторного мужского бесплодия необходима разработка и внедрение более результативных методов лечения.

Цель исследования. Оценить влияние низкоинтенсивной лазерной терапии (НИЛТ) в красном спектре на параметры эякулята, фрагментацию ДНК сперматозоидов (ФДНКС) и показатель MAR-теста у мужчин с идиопатическим бесплодием.

Пациенты и методы. Обследовали 85 мужчин с идиопатическим бесплодием, 50 из них (1-я группа) проводили курс НИЛТ, и 35 (2-я группа, контрольная) НИЛТ не выполняли. Средний возраст пациентов 1-й группы составил 31,4 ± 1,3 года, 2-й группы — 32,3 ± 1,4 года. НИЛТ проводили в красном спектре, на аппарате «Рубин-Ц» (Россия): 10 процедур через день по 10 мин на каждое яичко. До и после лечения оценивали гормональный статус, параметры спермограммы, MAR-тест, ФДНКС.

Результаты. НИЛТ у пациентов 1-й группы приводила к достоверному повышению объема эякулята, жизнеспособности сперматозоидов и количества их нормальных форм (в среднем на 11, 9 и 23 % соответственно), а также прогрессивной подвижности сперматозоидов в среднем на 14 и 19 % через 1 и 2 мес. соответственно. У 12 пациентов 1-й группы с изначально повышенной ФДНКС наступила ее нормализация после окончания лечения. Достоверное снижение MAR-теста выявили у пациентов 1-й группы с исходным уровнем данного показателя менее 30 %. В результате лечения беременность наступила у 10 из 50 (20 %) супружеских пар. У пациентов 2-й группы значимых изменений параметров эякулята и концентрации гормонов в плазме крови в течение 2 мес. наблюдения не возникало; беременностей в браке не наступило.

Выводы. НИЛТ в красном спектре приводит к достоверному улучшению качества эякулята при идиопатическом мужском бесплодии, нормализации патологической ФДНКС, снижению показателя MAR-теста.

Ключевые слова: мужское бесплодие; низкоинтенсивная лазерная терапия; красный спектр.

INTRODUCTION

Currently, about 15%–25% of married couples worldwide suffer from infertility. The male factor of infertility accounts for up to 50% of cases of sterile marriages [1]. In recent decades, there has been a significant decrease in fertile potential and deterioration in spermatogenesis in healthy men of reproductive age [2]. Despite numerous studies and advances in the diagnostics of male infertility, a significant proportion of cases of secretory pathozoospermia remain idiopathic. Idiopathic male infertility is characterized by impairment quantitative and qualitative parameters of the spermogram in the absence of risk factors for male infertility, disorders based on the physical examination, and changes in endocrine, genetic, and biochemical parameters [3].

There are no specific treatment methods for idiopathic male infertility. Patients are first recommended to adjust their lifestyle in order to minimize chronic intoxication and other harmful effects on spermatogenesis. A study conducted by members of the American Urological Association showed that two-thirds of practitioners use empirical drug therapy, including antiestrogens, aromatase inhibitors, and gonadotropins, to treat idiopathic pathozoospermia [4]. However, due to the lack of indisputable efficacy of gonadotropins, their use is not recommended by the European Association of Urology for idiopathic pathozoospermia [5]. The efficacy of antiestrogens (clomiphene citrate, tamoxifen) is based on the mechanisms of blocking cytoplasmic estrogen receptors in the hypothalamus, which results in increased production of gonadotropin-releasing hormone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), which then results in stimulation of spermatogenesis processes [6]. However, there are no reliable placebo-controlled studies demonstrating the efficacy of these drugs in this group.

Because one of the important pathogenetic mechanisms that reduce male fertility is the overproduction of reactive oxygen species, antioxidant therapy, given for no less than 3 months, is often used to treat idiopathic male infertility [3, 6]. Despite the fact that a number of studies have demonstrated the efficacy of this group of drugs, only 50% of men who seek medical help for idiopathic infertility can be treated using medication, while the rest typically require expensive procedures of assisted reproductive technologies [7].

Low-level laser therapy (LLLT), a physiotherapeutic method of treatment based on the medical use of light that does not cause tissue heating from laser optical radiation sources, is increasingly being used in andrological practice. Low power lasers are used for LLLT, with the most commonly used lasers operating with the red spectrum (with a wavelength of 600–700 nm) and the near infrared spectrum (with a wavelength of 710–1000 nm) [8]. The main advantages of LLLT include non-invasiveness, safety, a relatively low cost of procedures, and high efficacy [9].

The influence of LLLT in the red spectrum on the parameters of ejaculate in tests and clinical practice has been studied since the late 1980s [10–12].

Most of the works published in Russian and international literature are focused on assessment of the effect of low-intensity laser radiation on sperm motility, and only a few works discuss morphology, pathological sperm DNA fragmentation (SDNAF), and the level of antisperm antibodies in the ejaculate [9–11, 13–18].

This study aimed to assess the effect of LLLT in the red spectrum on the parameters of ejaculate, SDNAF, and the MAR-test index in men with idiopathic secretory infertility.

PATIENTS AND METHODS

The study included 85 men with idiopathic secretory infertility. Group 1 consisted of 50 patients who underwent LLLT. Group 2 (control) consisted of 35 men who did not receive LLLT. The average age of patients was 31.4 ± 1.3 years in group 1 and 32.3 ± 1.4 years in group 2. The average duration of infertility in marriage was 2.4 ± 0.7 years in group 1 and 2.5 ± 0.6 years in group 2.

All patients underwent examination, which included history taking, physical examination, semen analysis, detection of antisperm antibodies in the ejaculate (MAR-test), determining the degree of SDNAF by flow cytometry (Sperm Chromatin Structure Assay, SCSA), and analyzing the concentration of hormones in the blood plasma, namely total and free testosterone, LH, FSH, prolactin, estradiol, and globulin that binds sex hormones. The standard values for total and free testosterone in blood plasma were considered 6.07–27.1 nmol/L and 3.47–98.0 pmol/L, respectively.

Inoculation of ejaculate for opportunistic flora and/or analysis of ejaculate by the Androflor method using RT-PCR (real-time polymerase chain reaction) were performed to rule out inflammatory diseases of the male genital organs. The levels of tumor markers in blood plasma (AFP, LDH, β-hCG, PSA) were determined to rule out neoplasms of the testicles and the prostate gland. All patients underwent ultrasound examination of the scrotum organs using the color Doppler mapping mode.

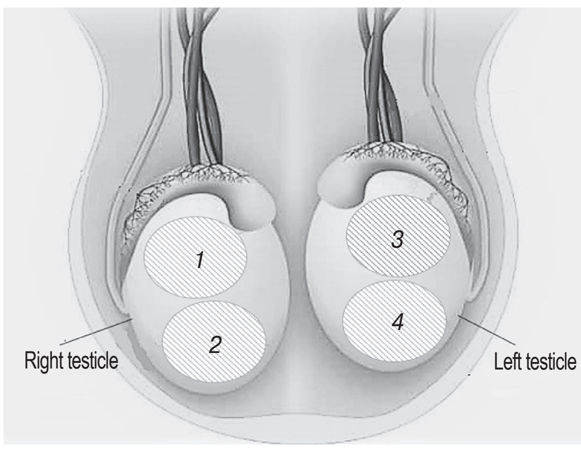
Spermogram results were assessed in accordance with the criteria of the World Health Organization 2010 [19]. When evaluating the ejaculate, the main parameters were concentration, progressive motility of spermatozoa (motility categories of classes A + B), and the number of normal forms of spermatozoa. Sperm morphology was assessed using strict criteria for Kruger fine morphology. The normative indicator of SDNAF was considered 15% or lower, and the normative indicator of the MAR-test was considered 10% or lower [20].

The criteria for inclusion in the study were infertility in marriage, age of 18 to 40 years, abnormalities of spermogram parameters (oligo- and/or astheno-, and/or teratozoospermia), an increase in SDNAF of more than 15%, and/or an increase in MAR-test more than 10%.

The exclusion criteria were azoospermia, hemospermia, stage 2–3 varicocele, signs of retrograde blood flow in color Doppler mapping mode, hydrocele, inflammatory diseases of the urethra and male genital organs in the phase of active inflammation, neoplasms of the scrotum or prostate, and/or severe concomitant pathology (hyperthyroidism, diabetes mellitus, etc.).

After the examination, patients in group 1 underwent LLLT in the red spectrum on a Rubin-C device (Russia) with the wavelength of 630 nm, power flux density of 13 mW per 1 cm^2, and energy density of 1.05 J/cm^2. Ten procedures were performed every other day. Each testicle was exposed through the skin at two points with an exposure of 5 minutes each (Fig. 1).

Immediately after the course of procedures, after 1 and 2 months, all patients underwent control examination that included semen analysis, MAR-test, determination of the SDNAF degree, and assessment of hormonal state. Statistical analysis of the data obtained was performed using the Statistica for Windows, v. 6.



Schematic representation of the zones of exposure to low-level laser radiation. The sequence of impact on the parenchyma zones of the right (*1*, *2*) and left (*3*, *4*) testicles is shown
Схематическое изображение зон воздействия низкоинтенсивного лазерного излучения. Показана очередность воздействия на зоны паренхимы правого (*1*, *2*) и левого (*3*, *4*) яичек

RESULTS

One month after the LLLT course, patients in group 1 experienced a significant increase in ejaculate volume and sperm viability, on average by 11% and 9%, respectively. By the end of month 2 after the treatment, the above parameters decreased insignificantly, but the ejaculate quality remained better than before the treatment. The average indicators of sperm concentration after the LLLT course did not change, while the progressive sperm motility increased on average by 14% and 19% after months 1 and 2, respectively. The number of normal forms of spermatozoa increased by the end of the treatment course, on average by 23%; this positive effect persisted at the end of month 2 of follow-up. This information is presented in Table 1.

Thus, the course of LLLT in patients of group 1 contributed to significant improvement in the main parameters of ejaculate, as well as to an increase in the total and free fractions of testosterone. The average SDNAF indices in group 1 patients before and after the LLLT course were within the normal values, but they decreased after the course of laser therapy. The best effect was noted 2 months after the LLLT course, when the decrease in the values of this indicator averaged 42% (Table). In 12 patients with initially elevated level of SDNAF, it returned to normal after the treatment. In two patients, a minor increase in SDNAF was noted 1 month after the LLLT course, followed by its normalization by the end of month 2 after the laser therapy.

In patients of group 1, the MAR-test value on average decreased immediately after the LLLT course and continued to decrease over the subsequent 2 months of follow-up (Table). However, we detected a significant decrease in the MAR-test values only in patients with an initial level of this indicator less than 30%.

In group 1, LLLT resulted in a significant increase in the average values of total and free testosterone fractions in blood plasma, and this effect persisted for 1 month during the follow-up (Table). No significant changes were observed in the concentration of all other hormones determined in patients of group 1 before and after the course of laser therapy.

The treatment for men in group 1 resulted in the onset of pregnancy in 10 (20%) of 50 married couples. No side effects or complications were noted during LLLT procedures or follow-up.

In patients of group 2 (control), after the course of treatment, a minor and insignificant decrease in the concentration of spermatozoa in the ejaculate was noted. At the same time, the rest of the spermogram parameters, the level of the MAR-test and SDNAF, as well as the concentration of all hormones in the patients' blood plasma before and during the 2 months after laser therapy did not change significantly. No pregnancies occurred in married couples.

The effect of low-level laser therapy on sperm parameters and testosterone concentration in blood plasma in patients of the group 1, *M* (SD)

Влияние низкоинтенсивной лазерной терапии в красном спектре на показатели эякулята и концентрацию тестостерона у пациентов 1-й группы, *M* (SD)

Parameters	Before treatment	Immediately after the LLLT course	1 month after the LLLT course	2 months after the LLLT course
Ejaculate volume, ml	3.2 (1.6)	3.4 (1.5)	3.6 (1.5)*	3.5 (1.6)
Sperm concentration, mln/ml	69.1 (58.1)	70.0 (49.4)	68.7 (48.5)	71.4 (50.6)
Number of progressively mobile forms of spermatozoa, %	33.5 (14.7)	35.8 (13.2)	38.1 (12.5)**	39.9 (9.3)**
Sperm viability, %	64.7 (12.7)	70.3 (10.9)*	66.4 (9.7)	64.9 (12.3)
Number of morphologically normal forms of spermatozoa, %	3.3 (2.2)	3.8 (2.0)*	3.6 (1.9)	3.7 (1.9)*
SDNAF, %	11.9 (7.9)	9.0 (4.6)**	7.6 (3.7)**	6.8 (3.3)**
MAR-test, %	4.6 (8.2)	4.4 (9.7)	0.8 (2.1)**	0.5 (1.8)**
Total testosterone, nmol/L	16.8 (7.3)	17.8 (6.1)*	18.1 (6.9)*	17.3 (7.1)
Free testosterone, pmol/L	42.1 (13.5)	46.0 (13.6)*	47.2 (12.8)*	43.6 (12.5)

Note. LLLT – low-intensity laser therapy. SDNAF – sperm DNA fragmentation. *The difference in parameters before and after treatment is significant ($p < 0.05$); **the difference in parameters before and after treatment is significant ($p < 0,01$).

DISCUSSION

Studies on the effect of laser radiation on spermatozoa have revealed that light energy is absorbed by human spermatozoa in highly restricted ranges, with maximum absorption in the red and infrared regions of the light spectrum [11, 12]. Spermatozoa can be stimulated both *in vitro* and *in vivo* by irradiation of the testicles and their appendages [12]. In this case, the LLLT efficacy depends mainly on the properly selected radiation parameters and the technique of laser exposure [21].

In our work, the energy density of laser radiation was 1.1 J/cm^2 with an exposure of 5 minutes per one point. It has been experimentally established that energy density of radiation up to 0.6 J/cm^2 has no detectable effect on spermatozoa; energy density from 0.6 to 1.2 J/cm^2 is energy-stimulating (increases fructolysis and oxidative activity of spermatozoa), while higher energy density produces a depressing effect [12]. However, to achieve a stimulating effect during LLLT, in addition to the energy density, the power density of laser radiation and the exposure time must be taken into account [21]. In a study by O.A. Giesinger et al [9], the native sperm of men was exposed to laser with a wavelength of 632 nm for 3 minutes, with the energy density of radiation of 1.1 J/cm^2. The exposure resulted in an increase in the number of actively motile forms of spermatozoa, as well as improvement in their respiratory activity. As a result, it was revealed that low-intensity laser radiation has a positive effect on the functional and metabolic state of spermatozoa.

The response of the cells to laser exposure in the red spectrum of radiation has been studied for many years. It is currently believed that the pathogenetic mechanism of LLLT action is based on the ability of light to change cell metabolism as a result of its absorption by mitochondria, particularly by cytochrome C oxidase. Cytochrome C oxidase is the main primary photo acceptor for laser radiation in the red spectrum. Its activation increases the production of ATP, and stimulates energy supply and consumption of Ca^{2+} by mitochondria, which ultimately leads to improvement in sperm motility and an increase in their fertile potential [14, 15, 22, 23]. Other photo acceptors are hemoglobin, cyclic nucleotides, iron, and copper, which contain enzymes of the redox cycle (catalase, superoxide dismutase). Catalase activity increases as a result of laser exposure in the red spectrum, which has a positive effect on the antioxidant system of the body, followed by a cascade of beneficial physiological reactions. The reactivation of superoxide dismutase leads to an increase in the antioxidant state in tissues, and a decrease in the level of lipid peroxidation. It is important to note that the above mechanisms contribute to microcirculation normalization in the tissues of the testicles, and to improvement of intraorgan hemodynamics, which stimulates the spermatogenesis processes [24].

The significant improvement in progressive sperm motility after the course of LLLT in the red spectrum, noted in our study, was also published in the works of other authors [14, 15, 17, 24, 25]. One of the first studies of the effects of light stimulation of human spermatozoa with subsequent assessment of their motility was conducted in 1984 by H. Sato et al [10]. The authors exposed male ejaculate (in the red spectrum, wavelength 647 nm) to laser irradiation with different intensities (4, 8, and 32 J/cm^2), and revealed that the total motility of sperm increased, to a greater extent (by 8%–10%) at the intensity of 32 J/cm^2. D. Preece et al [15] also found that stimulation with red light by a diode laser (wavelength 633 nm, power density 5.66 mW/cm^2) for 35 minutes resulted in an increase in sperm motility. In another work, laser exposure to ejaculate with a light-emitting diode with an exposure of 2, 5, and 10 minutes (wavelength 636.6 nm, output power 1.3 mW) increased significantly the sperm motility in patients with asthenozoospermia. The best effect was noted with an exposure of 5 minutes [14]. The results of our study demonstrated that LLLT in the red spectrum improves sperm motility significant, and also improves their viability, morphology, and ejaculate volume. The power flux density of the laser radiation was 3.56 mW/cm^2 with the radiation time of 5 min for each zone. We revealed no significant increase in the concentration of spermatozoa during the laser therapy.

It is currently known that under the influence of laser energy in the red spectrum, small amounts of reactive oxygen species (ROS) are produced in cells as a result of light absorption by endogenous porphyrins, mitochondrial cytochromes, and flavoproteins. It has been established that relatively low ROS concentrations play an important role in the activation of many cellular processes. In spermatozoa, ROS, such as superoxide anion, H_2O_2, and nitric oxide, induce capacitation and acrosome reaction [13, 15]. Y.J. Suzuki et al [26] revealed that ROS stimulate signal transduction processes to activate transcription factors, gene expression, and cell growth.

High concentrations of ROS are known to be able to cause damage to cell DNA [6, 27]. It was found that low-intensity laser radiation promotes the formation of ROS in an amount insufficient to damage DNA. D. Preece et al [15] found that laser exposure to spermatozoa in the red spectrum with a wavelength of 633 nm for 30 min (power density 31 mW/cm^2) does not cause double-stranded DNA breaks, and does not induce oxidative damage to sperm DNA. In another work, the authors evaluated DNA fragmentation (by SCSA) and did not reveal any damage to the integrity of the DNA structure, or an increase in the degree of its fragmentation after exposure to sperm with a laser with a wavelength of 660 nm and a high energy density [16]. These results are similar to those obtained by N. Salama et al [14], who did not reveal a negative effect on DNA condensation in male spermatozoa when stimulated with light using an LED laser (wavelength 636.6 nm, output power 1.3 W). The results of our work are similar to those described above; however, two patients had a minor increase in SDNAF one month after the course of laser therapy, which normalized by the end of month 2 of follow-up.

The efficacy and safety of low-intensity laser radiation have been studied previously in experimental studies [28]. Thus, J.-Ch. Ahn et al [29] conducted a histological examination of testicular tissue in laboratory animals after laser exposure and revealed no teratogenic or mutagenic effects in it. The authors also found that low-intensity laser exposure to the testicular tissue of rats in the red spectrum with a wavelength of 670 nm led to an increase in testosterone levels in the blood plasma. In our study, LLLT increased the values of the total and free fractions of endogenous (intrinsic) testosterone in the blood plasma of men, which undoubtedly contributed to improvement of spermatogenesis processes and, as a consequence, spermogram indices, primarily sperm motility.

After the LLLT course in the patients in our study, we noted a significant decrease in the MAR-test index with its initial value less than 30%, which, in our opinion, was the result of stabilization of the membrane potential of spermatozoa under the influence of laser radiation. This hypothesis needs to be further investigated. No studies on the influence of LLLT in the red spectrum on the MAR-test dynamics have been found in the available Russian and international literature.

CONCLUSIONS

1. LLLT in red spectrum leads to a significant improvement in the quality of ejaculate and the main parameters of the spermogram in idiopathic male infertility, which contributes to the onset of spontaneous pregnancy in marriage.

2. LLLT in red spectrum contributes to normalization of pathological SDNAF.

3. LLLT in red spectrum contributes to a decrease in the MAR-test index, if its initial value does not exceed 30%.

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