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Male autoimmune infertility: analysis of results and prediction of efficacy of low-level laser therapy in infrared spectrum

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INTRODUCTION: Autoimmune infertility is diagnosed in 5–15% of men. Currently applied methods of medical therapy of autoimmune male infertility are not very effective, which requires the development of new ones and creation of predictive algorithms for their efficacy.

The aim of our study was to evaluate the influence of low-level laser therapy (LLLT) in infrared spectrum on MAR-test rate and sperm fertile properties in men with autoimmune infertility, develop ways to predict the efficacy of this therapy.

PATIENTS AND METHODS: 47 men with autoimmune infertility were examined. 31 of them (1st group) underwent course of LLLT in infrared spectrum (10 procedures), and 16 patients (2nd group, comparison) had placebo-laser therapy sessions (10 procedures). MAR-test value, main semen parameters and sperm DNA fragmentation were assessed before and after the treatment. For creation of LLLT efficacy algorithm we used discriminate analysis.

RESULTS: In patients of the 1st group we indicated statistically significant decrease of MAR-test by an average of 19% immediately after the course of procedures, and by 33% – within two months after the end of the treatment, at its initial level 60% or lower. LLLT contributed to improvement of the semen fertile properties, pregnancy developed in the natural reproductive cycle in 19% of couples. We developed math model for prediction the efficacy of LLLT in infrared spectrum of autoimmune male infertility.

CONCLUSION: LLLT in infrared spectrum of male autoimmune infertility leads to MAR-test value decrease at its initial level less than 60%; improves sperm fertile properties. It is appropriate to use before LLLT predictive algorithm of its efficacy developed by us.

Keywords: autoimmune male infertility; MAR-test; low-level laser therapy; infrared spectrum.

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Аутоиммунное мужское бесплодие: анализ результатов и прогнозирование эффективности низкоинтенсивной лазерной терапии в инфракрасном спектре

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Введение. Аутоиммунное бесплодие диагностируют у 5–15 % мужчин. Применяемые в настоящее время методы консервативного лечения при аутоиммунном мужском бесплодии малоэффективны, требуется разработка новых методик, а также создание алгоритмов прогноза их эффективности.

Цель исследования: оценить влияние низкоинтенсивной лазерной терапии (НИЛТ) в инфракрасном (ИК) спектре на показатель MAR-теста и фертильные свойства эякулята у мужчин с аутоиммунным бесплодием, разработать способы прогнозирования эффективности данной терапии.

Пациенты и методы. Проведено обследование 47 мужчин с аутоиммунным бесплодием: 31 пациенту (1-я группа) проводили курс НИЛТ в ИК-спектре (10 процедур), а 16 пациентам (2-я группа, сравнения) — сеансы плацебо-лазеротерапии (10 процедур). До и после лечения оценивали величину MAR-теста, а также основные параметры спермограммы и фрагментацию ДНК сперматозоидов. Для создания алгоритма эффективности НИЛТ использовали дискриминантный анализ.

Результаты. У пациентов 1-й группы было отмечено статистически достоверное снижение показателя MAR-теста в среднем на 19 % сразу после курса процедур НИЛТ и на 33 % — через 2 мес. после окончания лечения, при исходном значении данного показателя 60 % или менее. НИЛТ приводила к улучшению фертильных свойств эякулята, беременность в естественном репродуктивном цикле наступила у 19 % супружеских пар. Разработана математическая модель прогнозирования эффективности НИЛТ в ИК-спектре аутоиммунного мужского бесплодия.

Заключение. НИЛТ в ИК-спектре аутоиммунного мужского бесплодия приводит к снижению величины MAR-теста при его исходном уровне менее 60 % и улучшает фертильные свойства эякулята. Перед проведением НИЛТ целесообразно использовать алгоритм прогноза ее эффективности.

Ключевые слова: аутоиммунное мужское бесплодие; MAR-тест; низкоинтенсивная лазерная терапия; инфракрасный спектр.

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INTRODUCTION

Nowadays, male infertility is a relevant problem both in Russia and in other countries. The male factor accounts for 30%–50% of infertility cases in married couples [1, 2]. One of the causes of male infertility is an autoimmune reaction against spermatozoa and production of anti-sperm antibodies (ASA) (Ig A and G) in testicular tissues [3–5]. The presence of ASA in men with infertility problem was first described by Rumke and Wilson in 1954. Since then, the presence of ASA in the ejaculate has been regarded as an independent causative factor of infertility; it is diagnosed in 5%–15% and 1%–2% of men with and without infertility problem, respectively [3, 6–8]. Risk factors for the emergence of ASA can be inflammatory diseases of the male genital organs (such as orchitis and prostatitis), varicocele, testicular injury with or without post-traumatic orchitis, cryptorchism, bilateral or unilateral vasoresection, post-traumatic or post-inflammatory obstruction of the vas deferens, malignant and benign neoplasms of testicles, etc. [8, 9].

The generally recognized international standard for the detection of ASA in ejaculate is the mixed agglutination reaction through mixed antiglobulin reaction (MAR) test. This test determines the ratio of normal, actively motile forms of spermatozoa coated with ASA to the total count of spermatozoa with the same motility characteristics, expressed as a percentage. In cases with a low count of progressively motile forms of spermatozoa, the MAR test becomes impossible, so it is recommended to determine the total ASA and antibodies to testicular antigens in the blood plasma [5, 7, 10].

Increased levels of ASA in the ejaculate causes agglutination of spermatozoa and, in some cases, disrupts their integrity, which results in a decrease in their motility and concentration. A possible reason of a decrease in the fertilizing ability of the ejaculate is the fixation of ASA to the surface of spermatozoa, which leads to their inability to penetrate into and fertilize the egg [3, 9, 11]. However, results of studies that have evaluated the effect of ASA on ejaculate parameters are contradictory; some of them indicate a significant deterioration in the main parameters of the ejaculate with ASA, while others do not [7, 9, 11, 12]. A meta-analysis conducted by Cui et al. [9], based on eight studies, showed that the concentration and count of progressively motile forms of spermatozoa (motility categories A + B) were significantly lower in the presence of ASA in the ejaculate than in their absence. In addition, ASA was found to have no significant effect on the morphology, viability of the spermatozoa, and volume of the ejaculate.

Bozhedomov et al. [11] revealed that a significant increase in the level of ASA in the ejaculate more often indicated pathological fragmentation of the sperm DNA. Thus, the percentage of spermatozoa with fragmented DNA was 1.3 times higher with an increased level of ASA in the ejaculate than without it ($p < 0.05$).

For the treatment of autoimmune male infertility, various conservative treatment options are employed; for example, glucocorticoids (prednisolone and methylprednisolone), antioxidants, enzyme preparations, and fetoplacental complexes are prescribed, and selective membrane plasmapheresis is initiated [8, 13, 14]. However, owing to the low efficiency and frequent side effects of these treatment methods, in most cases, infertility problems cannot be solved without the use of assisted reproductive technologies (ART) [8, 13]. In this regard, the search for new, more effective and safe methods of treatment of autoimmune male infertility is highly relevant.

In our earlier study regarding the efficiency of treatment of secretory male infertility using low-intensity laser therapy (LLLT) in the infrared (IR) spectrum, we recorded a decrease in the MAR test score in 11 of 12 patients who received treatment, which presented the potential of this method as treatment of autoimmune male infertility [15]. However, a small sample of patients with an increased MAR test score and the absence of a comparison group failed to assert the efficacy and safety of this treatment method for autoimmune male infertility; thus, it was not possible to develop personalized algorithms for predicting its efficacy, which caused initiation of this study.

This study aimed to assess the influence of LLLT in the IR spectrum on the MAR test score and the fertile properties of ejaculate in men with autoimmune infertility, to develop methods of predicting the efficacy of this therapy.

MATERIALS AND METHODS

This study is based on the results of examination and treatment of 47 men with autoimmune infertility. They were randomized into two groups. Patients of group 1 ($n = 31$) underwent a course of LLLT in the IR spectrum, and patients of group 2 (comparison group, $n = 16$) underwent placebo laser therapy. The average age of patients in group 1 was 33.4 ± 4.7 years and that in group 2 was 32.9 ± 4.3 years. The duration of infertility in group 1 was 2.1 ± 0.9 years and that in group 2 was 2.0 ± 0.7 years. All patients signed informed consent to participate in the study.

After history taking and physical examination, spermogram and MAR test were performed in all patients, the degree of sperm DNA fragmentation (SDNAF) was assessed by the sperm chromatin structure assay method. The spermogram was assessed in accordance with the World Health Organization recommendations in 2010 [10]; the normative value of the MAR test was considered ≤10%

and that of SDNAF was ≤15% [16]. The concentration of the following hormones in the blood plasma was determined: total and free fractions of testosterone, estradiol, prolactin, luteinizing hormone, follicle-stimulating hormone, and sex steroid-binding globulin.

The criteria for inclusion in the study were infertility in marriage, age 18–45 years, and an increase in the MAR test score of >10% in case of normozoospermia or pathozoospermia and a deterioration of the main parameters of the spermogram, namely, concentration of spermatozoa, count of progressively motile forms of spermatozoa, and/or count of normal forms of spermatozoa (oligospermia, asthenospermia, and/or teratozoospermia) with a normal or increased level of SDNAF.

The exclusion criteria for the study were azoospermia, hemospermia, varicocele, hydrocele, inflammatory diseases of the urethra and male genital organs in the phase of active inflammation, neoplasms of the scrotum or prostate gland, a history of trauma and surgery on the scrotum organs, and severe concomitant pathology (diabetes mellitus, etc.). To reveal the presence of inflammatory diseases of the male genital organs, all patients underwent ejaculate inoculation for opportunistic flora, and/or a molecular genetic study was performed using real-time polymerase chain reaction. For diagnosing neoplasms of scrotum organs and prostate gland, levels of tumor markers, including lactate dehydrogenase, alpha fetoprotein, β-human chorionic gonadotropin, and prostate-specific antigen, were determined in the blood plasma. All patients underwent ultrasound examination of scrotal organs, including Doppler blood flow imaging in the color Doppler visualization mode.

After the examination, patients of group 1 underwent a course of LLLT in the IR spectrum on the Rubin-C apparatus (Russia).

The wavelength of the laser radiation was 870 nm, and the energy density of the radiation was 1.1 J/cm^2. The course of treatment consisted of 10 laser therapy sessions, which were performed with 1 day interval. The influence was percutaneous, at 6 points, with an exposure of 1.5 min each, with a sequence on the zones of the parenchyma of the right (*1–6*) and left (*7–12*) testicles (Fig. 1).

Group 2 underwent 10 placebo laser therapy sessions with diode radiation turned off with 1 day interval. The zones and time of exposure of the right and left testicles were the same as that for group 1.

Control examination, which included spermogram, MAR test, SDNAF determination, and hormonal state assessment, was performed in all patients immediately after the course of procedures, as well as after 1 and 2 months.

Statistical analysis of data was performed using the Statistica for Windows computer program. The paired Student's test for normal samples and the paired Wilcoxon test for non-Gaussian samples were used for pairwise comparison of data before and after treatment in one group. Differences between the two groups were determined using the parametric Student's *t*-test or the Mann–Whitney rank test. Differences were considered significant at $p < 0.05$. Discriminant analysis was used to predict the efficiency of LLLT in normalizing the MAR test score.

RESULTS

Before treatment, the averaged MAR test scores were 41.8 ± 31.4% and 40.8 ± 33.2% in group 1 and group 2, respectively. In most patients of both groups, an increase in the MAR test score was accompanied by pathozoospermia, as well as pathological SDNAF. Figure 2 presents information on the incidence of

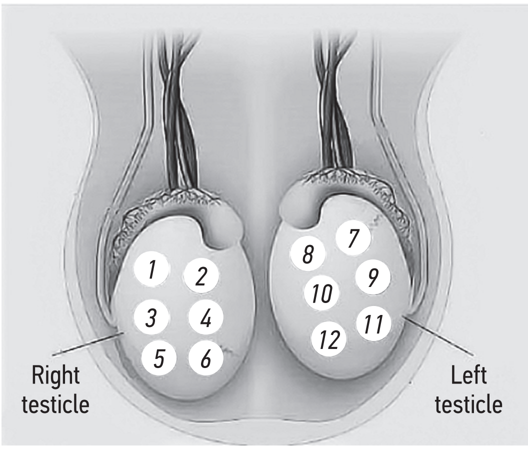

Fig. 1. Schematic representation of the zones of exposure to low-level laser irradiation in infrared spectrum on the tissues of the right and left testicles. *1–12* – sequence of impact zones

Рис. 1. Схематическое изображение зон воздействия низкоинтенсивного лазерного излучения в инфракрасном спектре на ткани правого и левого яичек. *1–12* — очередность зон воздействия

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normozoospermia and different variants of pathozoospermia in groups 1 and 2.

Before treatment in groups 1 and 2, asthenozoospermia and teratozoospermia prevailed, both separately and combined, while normozoospermia was determined only in 16% and 7% of the patients, respectively (Fig. 2).

An increased SDNAF level before the laser therapy was determined in 32% of men with autoimmune infertility in group 1 and in 38% of men in group 2. As a result of LLLT in the IR spectrum, patients of group 1 demonstrated a significant decrease in the MAR test score by an average of 19% immediately after treatment. The positive effect persisted for 2 months of follow-up, and after month 2, this indicator decreased by 31% (Fig. 3). Notably, a significant decrease in the MAR test score was noted only in patients with a baseline value of this indicator of ≤60%.

In addition, 1 month after the course of LLLT in group 1, we registered a significant increase in the concentration, progressive motility, count of normal forms, and viability of spermatozoa, in which improvement persisted until the end of second month of follow-up (Table 1).

As shown in Table 1, in group 1 patients with an initially increased SDNAF level, a decrease was noted immediately after the LLLT course, and after 1 month, it was normalized in 83% of patients, which persisted after the second month of follow-up.

The LLLT course in group 1 resulted in the onset of pregnancy in 6 (19%) of 31 married couples in the natural reproductive cycle. No side effects or complications were identified in the course of treatment and follow-up.

In group 2, after a course of placebo laser therapy and within 2 months of follow-up, no significant decrease in

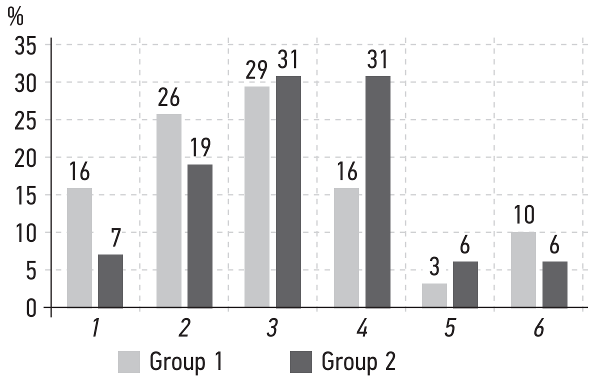

Fig. 2. Prevalence of different forms of pathozoospermia in patients of the 1st and 2nd groups. *1* – normozoospermia; *2* – asthenozoospermia; *3* – teratozoospermia; *4* – asthenoteratozoospermia; *5* – oligozoospermia; *6* – oligoasthenoteratozoospermia
Рис. 2. Частота встречаемости различных видов патозооспермии у пациентов 1-й и 2-й групп. *1* — нормозооспермия; *2* — астенозооспермия; *3* — тератозооспермия; *4* — астенотератозооспермия; *5* — олигозооспермия; *6* — олигоастенотератозооспермия

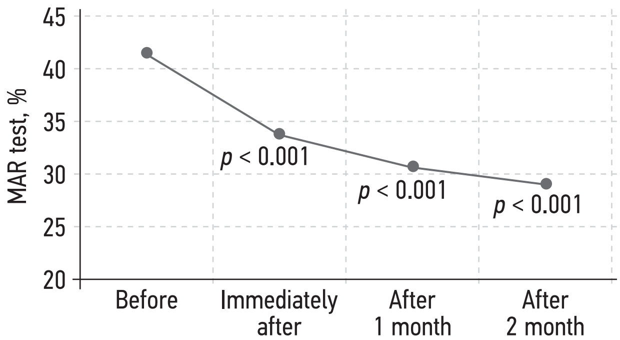

Fig. 3. MAR-test dynamics in the patients of the 1st group before and after the course of low-level laser therapy
Рис. 3. Динамика показателя MAR-теста у пациентов 1-й группы до и после курса низкоинтенсивной лазерной терапии

Table. Effect of low level laser therapy in the infrared spectrum on sperm parameters and pathological SDNAF in group 1, *M* (SD)
Таблица. Влияние низкоинтенсивной лазерной терапии в инфракрасном спектре на параметры спермограммы и патологическую фрагментацию ДНК сперматозоидов 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
Sperm concentration, mln/ml	61.4 (50.0)	60.3 (45.3)	71.1 (63.0) *	69.8 (54.4) *
Count of progressive motile forms of spermatozoa, %	33.2 (14.4)	35.0 (10.8)	37.9 (9.6) **	38.2 (9.5) **
Count of morphologically normal forms of spermatozoa, %	3.7 (1.9)	4.0 (1.7)	4.2 (1.9) *	4.1 (1.6) *
Sperm viability, %	63.1 (12.9)	64.0 (10.4)	67.2 (11.3) **	66.1 (10.6) *
Pathological SDNAF, %	20.9 (6.3)	15.5 (5.7) *	14.4 (2.3) **	11.5 (3.8) **

* The difference in indicators before and after treatment is significant ($p < 0.05$); ** the difference in indicators before and after treatment is significant ($p < 0.01$). *Note*. LLLT, low level laser therapy; SDNAF, sperm DNA fragmentation.

the MAR test score was recorded. For the entire 2-month follow-up period, the main parameters of the ejaculate and SDNAF value did not change significantly, and no pregnancies occurred.

Compared with placebo laser therapy, the efficiency of LLLT immediately after the treatment course was significantly higher in relation to the normalization of the MAR test score ($p < 0.001$) and pathological SDNAF ($p = 0.017$).

After 1 and 2 months of follow-up, the efficiency of LLLT was higher than that of placebo laser therapy in terms of a decrease in the MAR test ($p < 0.001$ and $p < 0.001$) and pathological SDNAF level ($p < 0.001$ and $p < 0.001$) and an increase in sperm concentration ($p = 0.048$ and $p = 0.004$), progressive motility ($p = 0.002$ and $p < 0.001$), and viability ($p < 0.001$ and $p < 0.001$).

Based on the results of discriminant analysis in group 1, we developed a mathematical model for predicting the efficiency of LLLT in the IR spectrum in relation to the MAR test score normalization in men with autoimmune infertility, taking into account the results of the pretreatment examination:

$$F = -0.077 \cdot \text{SpermMotilityProgressive0} + 0.112 \cdot \text{DurationDisease} + 0.027 \cdot \text{Ftest0} + 0.745 \cdot \text{SpermVolume0} - 0.057 \cdot \text{Mar0} - 0.999,$$

where F is the value of the discriminant function, SpermMotilityProgressive0 is the count of progressively motile forms of spermatozoa (%), DurationDisease is duration of the disease (months), Ftest0 is the concentration of free testosterone in blood plasma (pmol/l), SpermVolume0 is the ejaculate volume (ml), and Mar0 is the value of the MAR test indicator (%).

The threshold value was –0.0855. If the discriminant function (F) value after data substitution is greater than the threshold value, normalization of the MAR test score is predicted; if it is lower or equal to the threshold value, no effect is expected.

The canonical correlation coefficient was 0.932, Wilks' lambda was 0.132, and significance level was at $p < 0.001$. The specificity and sensitivity of the method were 92.9% and 87.5%, respectively, and the predictive ability of the presence and absence of an effect was 93.3% and 86.7%, respectively. Thus, the developed mathematical model has a high predictive value.

DISCUSSION

Autoimmune processes are caused by impairment of the mechanisms of emergence and maintenance of self-tolerance, that is, immune tolerance, to own antigens. Currently, a number of hypotheses for the induction of the development of autoimmune reactions have been proposed, including the theory of sequestered (hidden) antigens [13, 17]. When the immune system matures, the antigens of the genital glands are enclosed by the blood–testis barrier and are not in contact with blood plasma lymphocytes; as a result, they are not eliminated by the corresponding clones of immunocompetent cells. When the blood–testis barrier is disrupted and antigens enter the bloodstream, their own immunocompetent cells recognize them as foreign and trigger the immune response mechanism [13, 18].

Another theory of immunological regulation disorders is the decrease in the function of suppressor T-lymphocytes, dysfunction of T-helper lymphocytes, and impaired production of the corresponding cytokines by T-helper lymphocytes of types I and II [17].

An important factor in the development of autoimmune male infertility is oxidative stress, which is a result of an overproduction of reactive oxygen species. The latter disrupts the integrity of the sperm membrane and DNA structure, leading to a decrease in their motility and impairment of fertilizing ability [8, 13].

Previous studies have revealed that LLLT intensifies the processes of repairing DNA breaks, promotes the synthesis of repair enzymes and phospholipids and the formation of cell membranes, and activates the processes of reparative regeneration, proliferation of cell systems, and microcirculation [19–23]. In addition to the above-described effects, LLLT promotes the biosynthesis of antioxidant system substances and has an immunomodulatory effect [20, 24].

The mechanisms of action of LLLT on the human immune system have been investigated for many years. Laser therapy is able to stimulate immune responses and enhance the body's immunological adaptation [21]. In 1993, Tadakuma established that LLLT in the IR spectrum acted directly and selectively on the autoimmune system, restoring the immune competence of cells [24].

In our opinion, in addition to the sufficiently studied antioxidant and immunomodulatory mechanisms, a decrease in the MAR test score may be caused by the indirect effect of LLLT on the stabilization of the membrane potential of spermatozoa, which prevents the fixation of ASA on them, leading to agglutination and aggregation of spermatozoa. However, this hypothesis needs to be further investigated.

In our study, the reference value of the MAR test was ≤10%, and its increase was regarded as a sign of an autoimmune form of male infertility. Although the World Health Organization presented that the normal MAR test score is ≤50%, according to the Russian Society of Urology (2017), a MAR test value of >10% can be an indication for conservative treatment [10, 25]; with an increase to >50%, even with normozoospermia, the efficiency of conservative therapy is considered doubtful, and in most cases, the ART procedure (intracytoplasmic sperm injection (ICSI) into the egg) is recommended. According to Pochernikov et al. [4], the risk of pregnancy loss increased six times or higher with MAR test scores >10%. According to some authors, the MAR test value of 10%–50% is an indirect sign of the presence of inflammation of the urethra and male genital organs, but these patients were not included in our study.

The present study confirmed the efficiency of LLLT in the IR spectrum in men with autoimmune infertility; however, it resulted in a significant decrease in the MAR test score when its initial value was less than 60%. For the rest of the patients, we recommend ART, especially ICSI.

In most of our patients, an increase in the MAR test score before treatment was accompanied by pathozoospermia and/or pathological SDNAF, which coincides with the results of other studies [6, 11, 12]. Pathological SDNAF increases the risk of pregnancy loss due to the male factor both in the natural reproductive cycle and in in vitro fertilization/ICSI protocols [26, 27]. Interestingly, according to our data, LLLT not only led to an improvement in the fertile properties of the ejaculate by improving the main parameters of the spermogram, but also to the normalization of pathological SDNAF in most patients. Therefore, we recommend this treatment method when preparing men with autoimmune infertility for ART procedures, which will increase their efficiency and reduce the risk of pregnancy loss.

The mathematical model developed for predicting the LLLT efficacy in relation to normalization of the MAR test score has a high predictive ability of the presence and absence of effect, which was based on the results of routine laboratory studies prescribed to patients with male autoimmune infertility, can be used widely in clinical practice, and can be employed to achieve a personalized approach in choosing this type of treatment.

CONCLUSION

LLLT in the IR spectrum for autoimmune male infertility is more effective than placebo laser therapy. It leads to a decrease in the MAR test score at its initial level (<60%), increases the fertile properties of the ejaculate, and does not cause side effects. To resolve the issue of LLLT for a patient with autoimmune infertility, we recommend our prognostic algorithm to determine the efficiency of the forthcoming treatment.

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