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Стаття надійшла 1.09.2022 р.

DOI 10 26724/2079-8334-2023-3-85-166-170
UDC 616.44-089

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USING LASER PHOTODYNAMIC THERAPY IN THE TREATMENT OF AUTOIMMUNE THYROIDITIS

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The purpose of the study was to comparatively assess the effectiveness of treating patients with a diffuse form of autoimmune thyroiditis using laser photodynamic therapy and traditional treatment. The work was based on examination and treatment data of 90 patients in whom the concentrations of a number of hormones were examined: TSH, FT3, FT4, and Anti-TPO. In each group, the relative values of the analyzed indices, their mean error (m), and the reliability of intergroup differences (according to the χ^2 criterion) were calculated. Conservative therapy in patients of the control group brought a positive result only in 32 (64 %) patients, while in 18 patients out of 50 (36 %), signs of subclinical hypothyroidism, as well as structural changes in the thyroid gland, persisted in later dates (≥21 days). In the main group, hormone levels clearly improved, approaching normal values, indicating the absence of hypothyroidism signs in this group.

Key words: autoimmune thyroiditis, photodynamic therapy, photoditazine.

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ЗАСТОСУВАННЯ ЛАЗЕРНОЇ ФОТОДИНАМІЧНОЇ ТЕРАПІЇ ПРИ ЛІКУВАННІ АУТОІМУННОГО ТИРЕОЇДИТУ

Метою дослідження було проведення порівняльної оцінки ефективності лікування пацієнтів з дифузною формою аутоімунного тиреоїдиту із застосуванням лазерної фотодинамічної терапії та традиційним методом лікування. Робота ґрунтувалася на даних обстеження та лікування 90 пацієнтів, у яких було досліджено концентрацію низки гормонів: ТТГ, св. Т3, св. Т4 та АТ-ТПО. У кожній групі хворих розраховувалися відносні значення аналізованих показників, їхня середня помилка (m), 95 % довірчий інтервал (±2m) та достовірність міжгрупових відмінностей (за критерієм χ^2). Консервативна терапія у хворих контрольної групи принесла позитивний результат тільки у 32 (64 %) пацієнтів, у той час як приблизно у третини 18 (36 %) з 50 пацієнтів ознаки субклінічного гіпотиреозу, також, як і структурні зміни в щитовидній залозі, зберігалися і у пізніші терміни (21 днів і більше). У хворих основної групи показники гормонів явно покращали і наблизилися до показників нормальних цифр, що свідчить про відсутність у хворих цієї групи ознак гіпотиреозу.

Ключові слова: аутоімунний тиреоїдит, фотодинамічна терапія, фотодитазин.

The problem's urgency is due to the continuous growth of morbidity and insufficient effectiveness of existing treatment methods. The frequency of autoimmune thyroiditis reaches 25–35 % among all thyroid diseases and, after diabetes mellitus, ranks second among endocrinological diseases. Autoimmune thyroiditis (AIT) mainly affects the population aged 25 to 65 years [12, 14]. Long-term courses of conservative therapy have a temporary positive effect, but following the cessation of therapy, 40–60 % of patients have a relapse of autoimmune thyroiditis since the drugs help alleviate the symptoms but do not solve the real problem – the elimination of autoimmune inflammation [8, 10].

Long-term use of corticosteroids, which have immunosuppressive, anti-allergic, and anti-inflammatory effects, can lead to the development of the drug cushingoid, and these drugs do not prevent, but on the contrary, can aggravate hypothyroidism [1, 15]. The generally accepted treatment of the nodular and diffuse – nodular forms of autoimmune thyroiditis is surgical, and in the diffuse form of autoimmune thyroiditis, the treatment tactics depend on the degree of thyroid lesion and the prevalence of the pathological process [3]. Such patients have to go to different specialists in different clinics [2, 3]. Currently, most endocrinologists agree with the opinion of the urgent need to develop new methods and approaches to the treatment of this category of patients that can significantly optimize the results and, ultimately, significantly reduce the economic costs of treatment and reduce the rates of patient disability [7, 13].

In recent decades, there has been significant development and successful introduction of laser photodynamic therapy into the clinical practice of treating benign and malignant neoplasms of various localization, as well as inflammatory processes [5, 6]. Many authors note that the bactericidal effect of photodynamic therapy does not disappear with long-term treatment of surgical infections, while pathogenic microorganisms do not develop resistance to photodynamic therapy, regardless of the spectrum of sensitivity of pathogenic microflora to antibiotics [11, 14].

Photodynamic influence is local, and the bactericidal effect is limited to the zone of laser exposure, which allows avoiding many side systemic effects observed during antibiotic therapy [4, 9]. We think the anti-inflammatory and immunomodulatory effect of laser photodynamic therapy due to the release of cytokines and immune mediators is important, which makes it possible to attempt to study the possibility of using the laser photodynamic therapy method for treating the diffuse form of autoimmune thyroiditis. The diagnostic criteria, morphological changes, and treatment tactics in AIT are still not clear enough, despite the study of the main pathogenetic mechanisms. Thus, the increase in the frequency of AIT, the difficulties of diagnosis, and the conflicting opinions of researchers in approaches to the treatment of this category of patients indicate the relevance of this problem.

The purpose of the study was to perform a comparative evaluation of the effectiveness of treating patients with a diffuse form of autoimmune thyroiditis using laser photodynamic therapy and intravenous laser blood irradiation with low-energy laser radiation and the traditional method of treatment.

Materials and methods. The work is based on examination and treatment data of 90 patients. The examined and treated patients were two comparable, randomized groups: study (40) and control (50). In these patients, the concentration of a number of hormones was studied: TSH, FT_3, FT_4 and Anti-TPO. We compared the indices of the concentration of hormones in the blood in patients of these two groups on the 15th day of treatment. In the main group, the treatment of patients differed from those used in the control group in that with the beginning of conservative therapy, the patients underwent a session of laser photodynamic therapy, later on, the treatment of patients in both groups was identical, based on the methods of traditional therapy in combination with sessions of intravenous laser blood irradiation with low-energy laser radiation (ILBI-LILR).

The photodynamic therapy (PDT) technique was as follows. A patient with diffuse autoimmune thyroiditis on the second day of admission, 2–2.5 hours before the session, was injected intravenously with the photosensitizer “Photoditazin”-a chlorin E–6 derivative (“Veta Grand”) at a dose of 0.8 mg/kg on a physiological sodium chloride solution (NaCl 0.9 % –200.0).

To carry out photodynamic therapy, we used an AFS “Harmony” apparatus with an adjustable output power of up to 7 W and a radiation wavelength of 661±0.03 nm. The exposure time in continuous mode was 12–15 min at an energy density of about 25 J/cm^2. The distance between the fiber and the patient's neck was 20–25 cm. The patients of the main and control groups also underwent intravenous laser blood irradiation with the Solaris apparatus (λ=630 nm), the radiation power at the end of the fiber was 5mW, the exposure time was 20 min, 7–10 sessions were carried out per course. All patients tolerated sessions of laser photodynamic therapy and intravenous laser blood irradiation well, no patient had any complications. All patients with diffuse autoimmune thyroiditis in both groups received adequate complex therapy. Patients of the control group were given a course of conservative therapy in combination with sessions of intravenous laser blood irradiation with low-intensity laser rays (ILBI-LILR).

Levothyroxine preparations (euthyrox, L-thyroxine) were prescribed for replacement therapy at an approximate rate of 1.7 μg per 1 kg of the patient's body weight. The initial dose of the drug and the time to reach the full replacement dose were determined individually depending on age, body weight, and the presence of concomitant diseases, especially cardiovascular pathology.

To evaluate the effectiveness of the treatment, a fine-needle aspiration puncture biopsy (FNAB) was performed with cytological examination before the start of PDT, and then 5, 10, and 30 days after

treatment. The biopreparation was fixed in Carnois fluid for 2 hours and embedded in paraffin. Sections with a thickness of 5–7 μm were stained by Papanikolaou.

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Scientific Center of Surgery named after Academician M.A. Topchubashov, Republic of Azerbaijan, Baku (Minutes No. 2, dated May 16, 2019).

The obtained digital data were subjected to statistical processing using the methods of medical statistics. All calculations were carried out on the electronic spreadsheet EXCEL – 2019 and SPSS – 26. To evaluate the statistical significance of the differences in the frequencies of the studied symptoms, the non-parametric χ^2 criterion was used. Differences at $p<0.05$ were considered statistically significant. In each group of patients, the relative values of the analyzed indices, their average error (m), 95 % confidence interval (±2m), and the reliability of intergroup differences were calculated.

Results of the study and their discussion. The dynamics of the main indices of homeostasis demonstrated a more rapid normalization of the level of the content of leukocytes and blood lymphocytes in the main group of patients. With initially slightly increased levels of leukocytes and lymphocytes in the main and control groups, the decrease in this index for 4–5 days of treatment was: in the main group – 25,5 %, and the control group –12 %. Shifts of the leukocyte formula to the left during treatment showed the same tendency as the main one. ESR figures in patients of both groups with diffuse autoimmune thyroiditis were initially high: 26.5±5.2 mm/h. In the main group, the ESR figures on the 5th day decreased by 32.3 %, and on the 10th day, they returned to normal. In the control group, the dynamics were similar, but after 5 days it decreased by only 16 % in relation to the initial data, on the 10th day it decreased by another 48.5 %.

Thus, the obtained data on the dynamics of the leukocyte formula allows us to consider the results of the treatment of patients in the main group as more optimistic. The shift in the main biochemical parameters also indicated the advantages of using laser radiation in the diffuse form of autoimmune thyroiditis. The level of total blood protein in patients of both groups during the treatment period changed insignificantly and did not go beyond the physiological norm. The above can be attributed to the indices of AST and ALT, which did not demonstrate critical dynamics. We explain what has been said by the fact that all patients had an average severity of the clinical picture of the course of the disease. Changes in the level of total and direct bilirubin in the examined groups were within the limits of physiological values. The content of creatinine and urea in the blood was within the normal range.

In the main group, the level of C-reactive protein after 3 days decreased by 24.6 % in comparison with the initial data. In the control group of patients, this index decreased by 16 %, on the 10th day of treatment in the main group, this index corresponded to normal values, and in the control group, it exceeded the norm during this period by 8.5 %. A control ultrasound scan after 14 days of treatment in patients of the main group showed a pronounced positive dynamic – a decrease in the volume of the thyroid gland to normal values, resolution of the inflammatory process, the tissue structure became more uniform, an improvement in echogenicity was noted, which may indicate an improvement in the morphological structure of the thyroid gland. In patients of the control group, the ultrasound picture was characterized by insignificant positive dynamics. At the beginning of treatment, in most patients, the cytological picture was characterized by moderate lymphoplasmacytic infiltration of the glandular stroma, expressed to varying degrees in different parts of the gland with the presence of Ashkenazi – Hurthle cells. 5 days after laser photodynamic therapy, cytological studies show a significant weakening of lymphoplasmacytic infiltration of the thyroid tissue by 40 %. In the control group, according to cytological and follow-up data, on the 7th day of treatment, a weakening of lymphoplasmacytic infiltration was noted by only 23 %.

To assess the effectiveness of PDT in combination with ILBI-LILR, we studied the parameters of thyroid hormones. The study was conducted on patients of the control (50) and main (40) groups. The concentrations of thyroid hormones (FT_3; FT_4), pituitary gland (TSH), and antibodies to thyroid tissues (Anti-TPO) in the blood serum of patients before and then on the 15th day after treatment were studied and compared. When analyzing the data, it was revealed that in patients of the main group, the indices of Anti-TPO, TSH, FT_4 and FT_3 clearly improved and approached normal figures, which indicates the absence of signs of hypothyroidism in patients of this group.

In patients of the control group, we noted some changes, primarily related to a decrease in the level of TSH (before treatment: 9.99±1.34 μIU/ml; on day 15 after treatment: 3.13±0.82 μIU/ml ($t=6.9$, $p\leq0.001$)) by 3.2 times, an increase of 1.58 times in the concentration of FT_3 (before treatment: 3.10±0.66 pmol/l; on day 15 after treatment: 4.89±0.86 pmol/l ($t=4.3$, $p\leq0.005$)), and a decrease in Anti-TPO values by 4.94 times (before treatment: 326.28±46.89 IU/ml; on day 15 after treatment: 65.95±9.31 IU/ml ($t=5.4$, $p\leq0.001$))

Table 1

Indices of hormone levels in patients with autoimmune thyroiditis before and then on the 15th day after treatment (average values)

Means	Before treatment (mean/min/max)		15 days after treatment	
	Control group (n=50)	Main group (n=40)	Control group (n=50)	Main group (n=40)
TSH μIU/ml norm 0.27–4.2	9.99±1.34 [6.04–11.85]	6.54±0.47 [5.65–7.54]	3.13±0.82 [1.49–4.77]	3.00±0.21 [2.58–3.42]
FT_4 pmol/l norm 12.0–22.0	6.69±1.36 [8.98–4.91]	10.20±205 [12.95–7.63]	16.40±1.39 [13.62–19.18]	19.15±1.52** [16.11–22.19]
FT_3 pmol/l norm 3.1–6.8	3.10±0.66 [4.38–2.07]	2.99±1.01 [4,53–1,47]	4.89±0.86 [3.17–6.61]	5.11±1.10 [2.91–7.31]
Anti-TPO <34 IU/ml	326.28±46.89 [248.03–399.02]	176.80±16.29 [147.3–205.0]	65.95±9.31 [47.33–84.57]	31.57±5.75 ** [20.07–43.07]

Note: p≤ 0,001** statistical significance of differences between the main and control groups

Statistical differences in the main group between the indices before and on day 15 after treatment were, respectively, t=8.39, p≤0.001; t=4.78, p≤0.001; t=3.51, p≤0.01 and t=1.42, p≥0.05. Statistical differences in the control group between the indices before and on day 15 after treatment were t=5.40, p≤0.001; t=4.37, p≤0.001; t=5.11, p≤0.001 and t=1.66, p≥0.05 (Fig. 1).

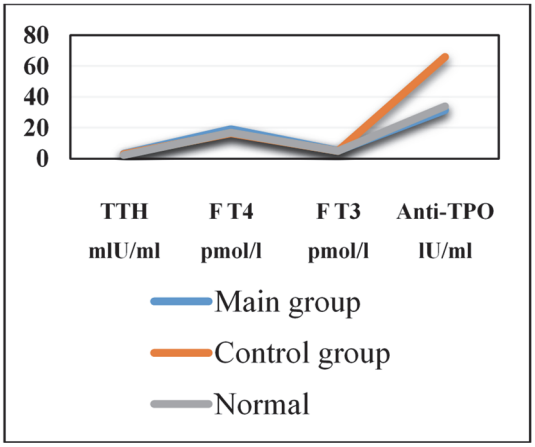

Fig. 1. Thyroid hormone levels at day 15 of treatment.

15 days after treatment, the average values of Anti-TPO in the second group are within the normal range (31.57±5.75 IU/ml), while the average values of Anti-TPO in the first group (65.95±9.31 IU/ml) exceed the norm by 1.9 times (t=3.15, p≤0.05)

The absence of signs of hypothyroidism in patients of the main group is also confirmed by clinical observations of patients and ultrasound data on the state of the thyroid gland (there are no signs of growth in the organ, changes in its structure and pathological changes in the form of the formation of hypo or hyperechoic areas, increased blood flow, the density and echogenicity of thyroid tissues decrease). In the control group, however, foci of hypo and hyperechogenicity in the segments of the thyroid gland and finely punctate hyperechoic inclusions due to compaction of the connective tissue remain. According to ultrasound, the thyroid tissue becomes more homogeneous and isoechoic. Hyperechoic strands (elements of intersegmental septa and vessel walls) become thinner or disappear. The volume of the gland approaches the individually optimal level.

Among patients in the control group, some changes were noted, primarily related to the increase in the level of TSH, a slight increase in the concentration of F T_3, and a decrease in Anti-TPO in about 2/3 of the observations. In patients of the first group, conservative therapy brought a positive result in only 32 (64 %) patients, while in 18 (36 %) of 50 patients, signs of subclinical hypothyroidism, as well as structural changes in the thyroid gland persisted at later dates (21 days or more). As a result, it was impossible to achieve complete rehabilitation of all 50 patients. Between the number of patients with positive results and the number of patients who failed to achieve full recovery, there are statistically significant differences (t=4.5, p≤0.001).

The obtained results clearly demonstrate the effectiveness of the complex application of the laser PDT method and intravenous laser blood irradiation with low-energy laser radiation ILBI-LILR in the treatment of diffuse AIT. Such treatment made it possible to reduce the duration of drug therapy and the average bed days in the absence of complications. Dynamic monitoring of patients with the study of homeostasis indices demonstrates the promise of using the laser PDT method developed by us in the complex treatment of AIT.

The results of the study indicate the ability to potentiate the effect of PDT in combination with traditional conservative therapy in patients with a diffuse form of AIT. Thus, the comparative analysis gives grounds to believe that the use of laser photodynamic therapy and intravenous laser blood irradiation with low-intensity laser rays has an absolute advantage over the use of traditional treatment methods. Analysis of the results obtained, based on the study of the developed method of non-pharmacological potentiation of the traditional treatment of autoimmune thyroiditis, it can be stated that the proposed complex method of supplementing traditional treatment with the use of laser photodynamic therapy and

intravenous laser blood irradiation with low-energy laser radiation sessions can effectively influence the autoimmune process and provide the best treatment results for this category of patients. Possessing a pronounced anti-inflammatory and immunomodulatory effect, the combined use of laser radiation, of course, contributes to the achievement of a favorable effect and a positive outcome in the treatment of the disease, which ultimately makes it possible to expand the arsenal of effective methods of treating autoimmune thyroiditis without increasing the pharmacological load on the patient.

According to the literature, the diffuse form of AIT occurs in approximately 40–60 % of patients [3]. Currently, treatment of the diffuse form of autoimmune thyroiditis is a rather complex problem in clinical medicine. There is a need for further research to improve treatment methods for patients with the diffuse form of autoimmune thyroiditis. [1, 13]. In recent years, there has been a successful application of laser photodynamic therapy (PDT) in clinical practice for the treatment of various dermatological and oncological diseases, as well as inflammatory processes of autoimmune origin [4, 6]. Our studies have confirmed the effectiveness of the combined use of laser PDT and intravenous laser blood irradiation with low-intensity laser rays (ILBI-LILR) in the treatment of patients with a diffuse form of AIT.

Conclusions

1. The obtained results clearly demonstrate the effectiveness of the complex application of the method of laser PDT and ILBI-LILR in the treatment of the diffuse form of AIT, which is also evidenced by indices of a reduction in the duration of drug therapy. A positive treatment result was achieved with conservative therapy only in 32 (64 %) patients; in approximately 18 (36 %) patients, signs of subclinical hypothyroidism, as well as structural changes in the thyroid gland, persisted even later (21 days and more) ($t=4.5$, $p\leq0.001$).

2. The proposed improved method using laser PDT and ILBI-LILR ensures the best treatment results for patients with diffuse autoimmune thyroiditis. Having a pronounced local effect on the cell-tissue structure of the thyroid gland, the combined use of laser radiation can ensure a favorable effect and a positive outcome in the treatment of the disease.

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Стаття надійшла 11.08.2022 р.