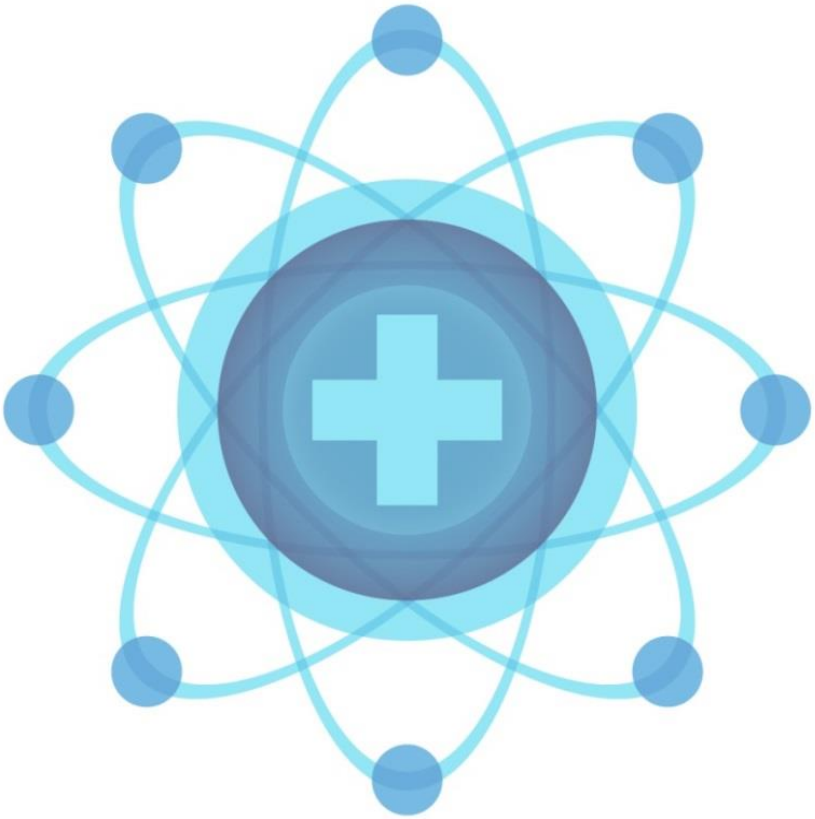

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THE EFFECTIVENESS OF PHOTODYNAMIC THERAPY IN THE CORRECTION OF CYTOKINE STATUS IN PATIENTS WITH CHRONIC SUPPURATIVE OTITIS MEDIA

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Abstract: The effectiveness of standard and combined treatment using photodynamic therapy was evaluated based on the study of the levels of interleukin-2, interleukin-6 and tumor necrosis factor in 84 patients with chronic purulent otitis media. Photodynamic therapy was administered with aqueous solution of methylene blue every other day for 6 days (3 manipulation. It was found that by the end of the course of traditional therapy, a cytokine imbalance persists, indicating ongoing inflammatory changes. The inclusion of photodynamic therapy in the treatment regimen of patients with chronic suppurative otitis media significantly improved cytokine status.

Keywords: cellular and humoral immunity, photodynamic therapy, chronic suppurative otitis media

Introduction. Chronic suppurative otitis media accounts for a significant part in the structure of diseases of the ENT organs and can lead to serious intracranial complications [2, 10]. It is known that one of the reasons for the formation of chronic suppurative otitis media is a change in immunity [1, 4, 7], in which cytokines play a binding role between leukocytes different classes [5, 11]. This encourages the inclusion of other types of treatment in the treatment regimen [4, 9, 12]. The theoretical prerequisites for the use of photodynamic therapy are the study of immune reactions in the context of the pathogenesis of diseases and laboratory evaluation of their effectiveness [3, 6].

Objective: to evaluate the effectiveness of standard and combined treatment with the use of photodynamic therapy in patients with chronic suppurative otitis media based on the study of levels of interleukin-2 (IL-2), interleukin-6 (IL-6) and tumor necrosis factor α (TNF).

Materials and methods. 84 patients with chronic suppurative otitis media aged from 19 to 69 years were treated. All patients underwent physical examination, X-ray or computed tomography of the temporal bones, general clinical laboratory tests, audiometry. According to the indications, surgical interventions were performed. The cytokine content was studied in blood serum by solid-phase enzyme immunoassay using test systems and reagents from domestic manufacturers. Blood sampling was carried out in the day of admission, the first day after surgery and before discharge. The preparation of blood serum samples was carried out according to the generally accepted method [8].

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All examined patients, depending on the activity of the inflammatory process, were divided into three groups. The first group consisted of 32patients with mesotimpanitis (code H66.1 according to the International Classification of Diseases) who received only conservative therapy. The second group there were 28people with epithympanitis (code H66.2), who simultaneously underwent sanitizing and functional operations on the middle ear. The third group included 24people with epithympanitis, who, due to the vastness of pathological changes (a significant amount of destructive destruction, large cholesteatoma, labyrinth fistula, sub- and epidural abscesses, facial nerve paresis), underwent only a sanitizing operation. The comparison group included 15 practically healthy people: 8 men and 7 women, without respiratory pathology, aged 18 to 45 years.

The efficacy of photodynamic therapy was studied by analyzing the amount of cytokines in two groups (42people each), in one of which photodynamic therapy was included in the standard therapy regimen and administered through the external auditory canal every other day for 6 days (3 manipulation).

The results of the study. Before the start of treatment, the titers of all tested cytokines depended on the severity of the inflammatory process. Thus, IL-2 indicators on the first day of hospitalization in patients of the first group were 1.6±0.14 pg/ml, in the second group – 2.6±0.38 pg/ml, in the third – 3.2±0.34 pg/ml.

Fluctuations in the level of this cytokine in the entire sample ranged from 0.1 to 8.3 pg/ml and averaged 2.6 ± 0.21 pg/ml. Elevated IL-2 levels above average were found in 31 patients with epithympanitis, 9 (42.8%) of them were from the second group, 22 (56.4%) - from the third (Table 1).

A similar dependence on the severity of the inflammatory process on the first day of hospitalization was found in the study of IL-6 and TNF. In the first group, the IL-6 titers corresponded to 3.2 ± 0.09 pg/ml, TNF α – 3.9 ± 0.35 pg/ml. In patients with epithympanitis, cytokine levels increase significantly: in the second group, IL-6 levels increase to 7.9 ± 0.79 pg/ml ($p < 0.05$ compared to the first group), TNF α to 6.0 ± 0.79 pg/ml; in the third group to 8.0 ± 0.53 pg/ml ($p < 0.05$ compared to the first group) and 6.1 ± 0.53 pg/ml, respectively. IL-6 levels are higher than the average for the entire sample (6.8 ± 0.4 pg/ml), so the same was found only in patients of the second (14 people) and third groups (22people). Above average (5.5±0.36 pg/ml) TNF α values on the first day of treatment were found in 42 patients, 6 cases from the first group – 18.75%, 14 patients from the second group – 50.0% and 15 people from the third– 62.5% (Table 1).

Table 1

Distribution of cytokines in patients with chronic suppurative otitis media depending on the severity of the inflammatory process

Clinical group		IL-2 (pg/ml)	IL-6 (pg/ml)	TNFa (pg/ml)
Group 1 (n = 32)	Admission	1,6 ± 0,14	3,2 ± 0,09	3,9 ± 0,35
	Extract	2,3 ± 0,17	3,9 ± 0,17	2,0 ± 0,20
Group 2 (n = 28)	Admission	2,6 ± 0,38	7,9 ± 0,79	6,0 ± 0,79
	Operation	4,6 ± 0,54	5,8 ± 0,48	3,4 ± 0,62

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	Extract	3,4 ± 0,40	5,8 ± 0,48	3,4 ± 0,62
Group 3 (n = 24)	Admission	3,2 ± 0,34	8,0 ± 0,53	6,1 ± 0,53
	Operation	5,8 ± 0,42	8,8 ± 0,33	7,5 ± 0,31
	Extract	4,3 ± 0,29	6,9 ± 0,37	5,1 ± 0,42
Control group (n = 15)		1,44 ± 0,06	1,1 ± 0,48	0,61 ± 0,2

Surgical trauma increases the concentration of IL-2, little changing the levels of proinflammatory cytokines. After surgery, the concentration of IL-2 increases almost twice, reaching 4.6 ± 0.54 pg/ml in patients of the second group, 5.8 ± 0.42 pg/ml in patients of the third group ($p < 0.05$ to preoperative figures). The indicators of IL-6 and TNF α in the early postoperative period do not change significantly, continuing to depend on the degree of the destructive process, and are determined in patients of the third group as higher – 8.8 ± 0.33 pg/ml and 7.5 ± 0.31 pg/ml (Table 1).

By the end of the course of treatment and discharge from the hospital, an increase in the concentration of IL-2 and a decrease in the serum content of IL-6 and TNF α were found in all clinical groups in comparison with the figures at the time of admission. During these periods of the disease, the dependence of the concentration of cytokines on the degree of the destructive process remained, their minimum numbers were determined
in patients of the first group, the maximum – in patients of the third group. So, in the first group, the levels of IL-2 by the time of discharge from the hospital were 2.3 ± 0.17 pg/ml, IL-6 – 3.9 ± 0.17 pg/ml, TNF α –2.0 ± 0.2 pg/ml ($p < 0.05$ to the figures at admission). In patients of the second group, titers were determined to be higher 3.4 ± 0.4 pg/ml, 5.8 ± 0.48 pg/ml and 3.4 ± 0.62 pg/ml, respectively, increasing in the third group to 4.3 ± 0.29 pg/ml, 6.9 ± 0.37 pg/ml and 5.1 ± 0.42 pg/ml, significantly differing for all tested cytokines from the levels in the first group ($p < 0.05$). In addition, regardless of the timing of testing, the levels of all cytokines differed markedly from those of the control group (Table 1).

The clear dependence of cytokine levels on the degree of the inflammatory process, the effect of surgical trauma on their indicators and the preservation of cytokine imbalance by the time of discharge from the hospital predetermined the inclusion of photodynamic therapy in the treatment regimen of patients with chronic suppurative otitis media.

In patients who received only traditional therapy, there was no significant dynamics in cytokino b levels by the time of discharge from the hospital. Thus, the titer of IL-2 in patients of this group at admission was 2.4 ± 0.26 pg/ml, at discharge – 2.8 ± 0.29 pg/ml, IL-6 – 6.6 ± 0.44 pg/ml at admission and 7.2 ± 0.46 pg/ml at discharge, TNF α – 5.3 ± 0.57 pg/ml and 5.9 ± 0.62 pg/ml. By the end of inpatient treatment (10-14 days of hospitalization), the levels of all tested cytokines significantly differed from those in the control group: IL-2 – $p < 0.05$, IL-6 – $p < 0.01$, TNF α –$p < 0.001$ (Table 2).

Table 2

Distribution of cytokines in patients with chronic purulent otitis media, depending on the inclusion of photodynamic therapy in the treatment regimen

Indicator		IL-2 (pg/ml)	IL-6 (pg/ml)	TNFa (pg/ml)
Standard therapy (n = 42)	Admission	2,4 ± 0,26	6,6 ± 0,44	5,3 ± 0,57
	Extract	2,8 ± 0,29	7,2 ± 0,46	9 ± 0,62
+Photodynamic therapy (n = 42)	Admission	2,6 ± 0,32	6,2 ± 0,51	5,4 ± 0,55
	Extract	4,0 ± 0,28*	**3,8 ± 0,22***	**1,3 ± 0,2***
Control group (n = 15)		1,44 ± 0,06	1,1 ± 0,48	0,61 ± 0,2

*Note: * - significant differences in the concentration of interleukins at admission and before discharge (p < 0.05); bold indicates significant differences in the titers of interleukins in the formed groups before discharge (p < 0.05)*

Photodynamic therapy included in the treatment regimen for chronic suppurative otitis media, significantly changed the cytokine status of patients discharged from the hospital. By the end of conventional therapy, the majority of patients had higher levels of IL-2 compared to the levels at the beginning of therapy. By the time of discharge, the average IL-2 indicators had increased by more than 1.5 times and amounted to 4.0 ± 0.28 pg/ml ($p < 0.05$ compared to the indicators in the control group) (Table 2, Fig. 1). Cytokine activation enhances local resistance, accelerates remission of chronic inflammation and prevents relapses of the disease.

The concentration of IL-6 when using photodynamic therapy significantly decreased by the end of the course of treatment and averaged 3.8 ± 0.22 pg/ml. This figure is 2 times less than the average values of the mediator at discharge in the group of patients treated according to the traditional scheme (7.2 ± 0.46, $p < 0.05$), and in 1.5 times less than the figures for admission to the hospital (6.6 ± 0.51 pg/ml, $p < 0.05$) (Table 2, Fig.).

Nevertheless, the average IL-6 indicators significantly exceed those in the group of healthy donors (1.1 ± 0.48 pg/ml), which may indicate ongoing inflammatory changes, even when

normalization of the objective status and otoscopic picture.

The dynamics of TNF α levels looks similar. In the group of patients with the use of photodynamic therapy by the end of the course of treatment, there was a noticeable tendency to normalize the indicators -1.3 ± 0.2 pg/ml, with levels in the control group – 0.61 ± 0.2 pg/ml. Significant differences with the levels of this cytokine were noted both at discharge in the group of patients receiving only traditional therapy – 5.9 ± 0.62 pg/ml ($p < 0.01$), and with the indicators at admission in the group of patients receiving combined photodynamic therapy – 5.4 ± 0.55 pg/ml ($p < 0.05$) (Table. 2, fig.).

Conclusion. By the end of the course of traditional therapy of patients with chronic purulent otitis media, cytokine imbalance persists, indicating ongoing inflammatory changes. The inclusion of photodynamic therapy in the treatment

regimen of patients with chronic suppurative otitis media made it possible to significantly improve the cytokine status.

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