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INFLUENCE OF ANAESTHESIA ON THE IMMUNE STATUS OF PATIENTS WITH MALIGNANT NEOPLASMS IN THE OROPHARYNGEAL REGION

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The immune system, as the main factor in protecting the body from the action of infectious, viral agents, as well as performing anticancer surveillance, undergoes a number of negative changes during surgery. With surgical intervention that causes a stress response and the effects of anesthetics, immunosuppression is formed, which in turn reduces the quality of medical care to patients, increases the duration of hospital stay, as well as the development of a number of complications. The purpose of the study was to evaluate the effect of pre-carbohydrate loading and perioperative administration of dalargin on immunity indicators in patients who underwent surgery for malignant neoplasms of the oropharyngeal region. Materials and methods. 58 patients operated on for malignant neoplasms of the oropharyngeal region were examined. Patients are divided into 2 groups. In the main group (n=29), patients received a carbohydrate load of 400 ml for 12 hours and 200 ml for 2 hours before surgery, used multicomponent general anesthesia with the introduction of dalargin at a dosage of 45-55 mcg/kg/min, at the end of the operation, dalargin was administered 1 mg intramuscularly. In the control group (n=29) was multicomponent general anesthesia. The morphological composition of blood, the content of cytokines (IL-1β, -6, -8, -10, INF-γ and TNF-α) and immunoglobulins (IgA, IgM, IgG) were determined. Results. The level of lymphocytes in the postoperative period up to 7 days was significantly higher in the main group than in the control group, where there was a decrease in this indicator relative to the preoperative level. A significant increase in rod-shaped neutrophils in the control group also persisted up to 7 days after surgery. On the 1st day after surgery, the cytokine content significantly increased in both groups. The values of IL-1ß, IL-6, IL-8, INF-γ, TNF-α were significantly higher in the control group, however, on the 7th day after surgery, significant differences between the groups remained only in the indicators of IL-8, INF-γ. When assessing the level of immunoglobulins, statistically significant differences were revealed between the groups – in the main group, the concentration of IgA on day 1 and IgG on day 7 after surgery was higher. The content of CRP in both groups increased significantly on the next day after surgery, and in the main group the indicators were statistically significantly lower compared to the control group. The level of CRP in both groups remained above the initial values up to 7 days after surgery. Conclusion. The use of enkephalin, dalargin, as a component of anesthetic support in the perioperative period in the surgical treatment of malignant neoplasms of the oropharyngeal region is associated with a lower concentration of pro-inflammatory interleukins, an increase in IgG concentration compared with endotracheal multicomponent anesthesia and may contribute to the activation of an antitumor immune response.

Keywords: dalargin, anesthesia, immunity, depression, stress protection.

Introduction. The state of the immune system is of great importance in the life of the human body, having a significant impact on the incidence of postoperative complications, the duration of postoperative rehabilitation, and, most importantly, can affect the final result of treatment of the underlying disease. On the other hand, the surgical stage of treatment can have a negative impact on the immune status of patients.

In modern medical practice, there is substantial and convincing evidence confirming the almost inevitable occurrence of postoperative immunosuppression [11]. Such immunodeficiency can manifest itself in varying degrees and is the result of a complex interaction of many factors.

Surgical methods of treatment, through the activation of various components of humoral and cellular immunity, are accompanied by local or systemic inflammatory reactions and lead to disturbances in carbohydrate metabolism - insulin resistance [14]. In this condition, excess glucose independently causes hyperproduction of proinflammatory cytokines [15]. This, in turn, increases catabolism and mobilization of energy substrates, which also negatively affects the patient's postoperative recovery and the prognosis of his treatment.

It is important to emphasize that a negative effect on the immune system is characteristic not only of surgical intervention, but also of anesthesia compo-

nents [10,6]. One of the leading roles in this is provided by analgesics – opioids. Despite the significant positive role of this group of drugs, without which it is impossible to carry out traumatic surgical interventions, they also have a number of disadvantages such as inhibition of phagocytosis by neutrophils, inhibition of the proliferative ability of macrophages, decreased production of anti-inflammatory cytokines IL-10 and IL-12, immunoglobulins, IL-2 , INF-γ, NK cell activity, and inhibition of lymphocytic proliferation [16,8]. All this, along with stimulation of angiogenesis [**19] is a significant factor in the suppression of the immune system and can contribute to the progression of the tumor process [13].**Consequently, the developed dysregulation of the immune system must be neutralized by choosing anesthetics that minimally inhibit immune reactions.

In the context of immunomodulation, an important link and mechanism that corrects the systemic inflammatory response to stress, prevents immunosuppression and increases the body's stress immunity is the use of a combination of a preliminary carbohydrate load and dalargin. The prerequisites for the use of dalargin in an anesthetic regimen were data on antinociceptive, antistress, immunomodulatory, and organoprotective effects [12,20]. In addition, a number of studies have confirmed the safety of using dalargin in cancer pathology [1].

Purpose of the study. To evaluate the effect of preoperative carbohydrate loading and stress protection with dalargin, as a component of anesthesia, on the immune status of patients with malignant neoplasms of the oropharyngeal region

Materials and methods. The presented work is a single-center prospective study. The formation of groups of patients was carried out using the case-control method. The study was conducted with permission from the local ethics committee of the Oncology Research Institute of the Tomsk National Research Medical Center (protocol No. 2 of 01/18/2023).

Inclusion criteria:

- availability of voluntary informed consent of the patient;
- diagnosis of cancer of the oral cavity and oropharynx T1-4 N0-3 M0 stage;
- patient age from 18 to 75 years;
- Class II–III according to the classification of the physical status of patients of the American Society of Anesthesiologists;
- areas of surgical intervention: oral cavity, oropharynx, +/- lymph node dissection of the neck (according to indications);
- normal white blood cell count.

Non-inclusion criteria:

- refusal of treatment;
- disseminated or inoperable tumor process;
- concomitant decompensated diseases;
- history of diabetes mellitus;
- emergency operations;
- perioperative blood transfusions.

The study included 58 patients (Table 1) with operable cancer of the oropharyngeal region who were treated at the Department of Head and Neck Tumors of the Oncology Research Institute of the Tomsk National Research Medical Center. Patients were comparable in age, anthropometric data and ASA.

The patients underwent the following surgical interventions as planned (Table 2):resection of the lower jaw with a reconstructive plastic component, glossectomy with reconstructive plastic component, wide excision of the cheek tumor with reconstructive plastic component, combined resection of the oropharynx. If indicated, lymph node dissection of the neck was performed on one or both sides. During surgical intervention, as well as in the postoperative period, there was no need for transfusion of blood components.

All patients were divided into 2 clinical groups, 29 people in each.

Characteristics of perioperative management. Preoperative preparation was carried out for patients of the main group. Zand 10-12 hours before surgery, patients received 400 ml of a carbohydrate drink (Provide Extra drink, Fresenius Kabi). 2-3 hours before surgery - another 200 ml. Premedication in both groups included diazepam solution 0.5% - 2 ml intramuscularly 30 minutes before surgery. Further anesthesia, after the administration of propofol 1.5-2 mg/kg, rocuronium bromide 0.6 mg/kg, was carried out with Sevoflurane 2.0-2.5 vol% (MAC 1.0) with a bolus injection of fentanyl 2-4 mcg /kg/ at the moment of the greatest stress response. The difference between the main group in the anesthetic care was that these patients, from the moment of admission to the operating room, received an intravenous infusion of dalargin at a dosage of 45-55 mcg/kg/h,and at the end of the surgical intervention, 1 mg of dalargin was administered intramuscularly once. Intraoperative monitoring was carried out according to the Harvard standard [8].

Determination of the morphological composition of blood was assessed during a general clinical blood test. Venous blood was collected: the day before surgery, immediately after surgery, 1 day after surgery, 7 days after surgery.

Determination of the concentration of cytokines (IL-1β, -6, -8, -10, INF-γ and TNF-α) and immunoglobulins (IgA, IgM, IgG) in blood serum was performed using test systems for enzyme immunoassay (JSC "Vector -Best", Russia). Blood

Table 1

Characteristics of the studied patients

Indicator	Main group (N=29)	Control group (N=29)
Age, years	60±8.5 years	59.6±9.3 years
Male/female, n (%)	15 (51.7) / 14 (48.3)	14 (48.3) / 15 (51.7%)
BMI,kg/m^2	24.5±2.7	25.2±3.1
ASA II/III, n (%)	21 (72.4) / 8 (27.6)	23 (79.3) / 6 (20.7)

Table 2

Scope of surgery

Operation name	Main group (N=29)	Control group (N=29)
Combined resection of the oropharynx	7 (24)	6 (20.7)
Combined resection of the tongue. floor of the mouth. lower jaw	8 (27.6)	9 (31)
Resection of the lower jaw	6 (20.7)	5 (17.2)
Tongue resection	6 (20.7)	5 (17.2)
Skin resection of the buccal area	2 (6.9)	4 (13.8)
Lymph node dissection of the neck	26 (89.7)	25 (86.2)

Table 3

Dynamics of leukocyte formula indicators

Indicator	Group	Before surgery	After surgery	1 day after surgery	7 days after surgery
Lymphocytes, %	Main	25.1±1.5	25±1.5 #. *	27±3.4 #	27.0±1.9 #
	Control	24.7±0.9	22.5±0.9 *	19.7±0.4 *	21±0.1 *
Neutrophils s/i, %	Main	52.0±6.4	52.1±6.4 #	54.7±6.2 #	54.5±3.3 #
	Control	50.4±6.8	49.7±0.9 *	59.3±0.8	57.2±0.5
Neutrophils p/i, %	Main	0.9±0.3	1.0±2.3 #	0.5±1.6 #,*	0.5±0.6 #,*
	Control	0.8±0.2	1.6±0.1 *	2.0±0.1 *	0.95±0.1
Monocytes, %	Main	5.8±2.1	5.8±0.5	6.0±1.1 #	4.6±1.5 #,*
	Control	5.9±2.4	5.9±0.2	4.5±0.5 *	4.5±0.1 *
Eosinophils, %	Main	2.4±0.5	2.5±0.3	2.5±0.4	3.1 ±0.4 *
	Control	2.3±0.2	2.4±0.1	2.5±0.1	3.3±0.2 *

* - p < 0.05 compared with the preoperative stage, # - p < 0.05 between groups

samples were collected in tubes containing ethylenediaminetetraacetic acid (preservative) and centrifuged for 10 min at 4°C immediately after collection. Venous blood samples were taken for immunity indicators: the day before surgery, 1 day after surgery, 7 days after surgery. All studies were performed on the day of blood collection.

For statistical analysis, the Microsoft Excel software package "Statistica 10.0" was used. Normality of distribution was assessed using the Shapiro-Wilk test. Depending on the distribution, the data were presented as arithmetic mean and standard deviation (M ± α). The significance of differences depending on the distribution was assessed using parametric and non-parametric tests: Student's t-test or Mann-Whitney U-test. To analyze qualitative characteristics, the χ2 test, χ2 test with Yates correction, or Fisher's exact test were used. P values <0.05 for all tests were considered statistically significant.

Results. Before anesthesia, the morphological composition of the blood of patients in both groups was homogeneous and did not have statistically significant differences (Table 3). The level of leukocytes in both groups during the entire evaluation period did not go beyond the normal range. However, after surgery, changes affected the percentage of lymphocytes: in the main group its value was significantly higher (25±1.5% versus 22.5±0.9% in the control group). 1 day after the operation, these changes, both in quantitative terms and in percentage, became more pronounced and also affected neutrophils and monocytes. The changes that occurred persisted up to 7 days after surgery.

Before anesthesia and surgery, the concentration of cytokines did not differ significantly between the groups (Table 4). On the 1st day of the postoperative period in both groups, the content of both anti- and proinflammatory cytokines increased significantly in comparison with the initial indicators and between groups. Values of pro-inflammatory cytokines IL-1β, IL-6, IL-8,INF-γ, and alsoTNF-αwere significantly higher in the control group. On the 7th day after surgery, significant differences between the groups remained only in IL-8,INF-γ.

The concentration of the anti-inflammatory cytokine IL-10 in the main and control groups one day after surgery significantly exceeded preoperative values. On the 7th day, the indicator decreased to initial values in both groups.

The levels of all immunoglobulins underwent changes at some stage of the study. However, statistically significant differences between the groups were recorded only in IgA on the 1st day and IgG on the 7th day after surgery.

The content of CRP in both groups on the next day after surgery increased significantly, and in the main group the values were statistically significantly lower compared to the control group. On the 7th day of the postoperative period, the level of CRP in both groups decreased, however, it was significantly higher compared to the initial values.

Discussion of results. Long-term surgical interventions in the oropharyngeal region are a stress factor and are accompanied by significant tension in all protective regulatory systems of the body, which is manifested by the development of a surgical stress response and, as a consequence, immunosuppression [3]. It has been demonstrated in animal models that areas of surgical trauma may be preferential sites for local tumor progres-

Table 4

Dynamics of immunity and CRP indicators

Indicator	Group	Before surgery	1 day after surgery	7 days after surgery
IL-1β, pg/ml	Main	3.5±0.7	6.6±2.5 #,*	3.4±0.9
	Control	3.3±0.6	9.4±1.4 *	3.4±0.7
IL-6, pg/ml	Main	4.0±0.9	20.3±9.3 #,*	4.3±1 *
	Control	4.2±0.9	40.3±6.2 *	4.6±0.9 *
IL-8, pg/ml	Main	3.5±0.6	8.7±2.7 #,*	3.5±0.8 #
	Control	3.4±0.5	15.2±1.6 *	3.9±0.6 *
IL-10, pg/ml	Main	3.0±0.4	19.2±3.8 *	3.0±0.5
	Control	2.8±0.6	18.4±5.5 *	3.1±0.6
INF-γ pg/ml	Main	3.1±0.9	5.4±2.3 #,*	4.4±1.4 #,*
	Control	3.3±0.7	8.7±1.9 *	6.3±1.0 *
TNF-α, pg/ml	Main	5.2±1.2	6.4±0.7 #,*	5.3±0.8
	Control	5.4±08	8.6±0.4 *	5.4±0.7
IgA, g/l	Main	2.7±1.0	2.5±0.8 #,*	2.7±1
	Control	2.3±1.1	1.7±0.9 *	2.2±0.9 *
IgM, g/l	Main	1.1±0.6	1.2±0.7	1.2±0.5
	Control	1.2±0.7	1.0±0.5 *	1.3±0.2
IgG, g/l	Main	10.6±2.2	10.8±2.0 *	11.3±2.1 #
	Control	10.2±2.3	9.4±2.2 *	9.2±2.0 *
SRB, mg/l	Main	15.7±7.9	35.2±41.9 #,*	17.7±16.1 #,*
	Control	20.1±7.2	68.5±22.4 *	29.8±11 *

sion, and it has previously been shown that surgery may indirectly stimulate the development of locoregional metastases [23]. A number of published studies describe that surgical trauma leads to systemic changes that accelerate tumor development [26,25]. Thus, surgery causes both local and systemic changes that may contribute to tumor progression. However, tumor cell migration during surgery alone cannot fully explain the high recurrence rate. The generally accepted opinion at the moment is that surgery inevitably leads to injury, which initiates a stress response covering a wide range of endocrinological, immunological and hematological consequences, and this in turn indirectly affects long-term surgical and oncological treatment results.

The anesthetics used also have a negative effect on the functioning of the immune system [24]. However, it should be noted that such effects are short-lived and of little significance for patients with a normal immune system. However, in patients with existing immune disorders, including cancer patients with previous chemoradiotherapy [17], as well as in high-risk patients, the influence of drugs in the anesthetic regimen may have important clinical implications for the perioperative period and immune imbalance.

During the study, there was a significant increase in the level of band neutrophils and a decrease in the content of one of the most important components of the immune system, lymphocytes, compared to the initial data in the control group immediately after surgery, which may indicate the presence of the most pronounced stress reactions in the perioperative period.

It is known that both surgical intervention and the components of anesthesia indirectly affect the appearance in the blood of certain cytokines that can regulate the processes of proliferation, differentiation, functioning, apoptosis of cells and can have a pro- or anti-oncogenic effect [2]. Although inflammation is a normal protective response to injury and infectious agents, tumor cells can use this process for their own survival and progression [21]. In addition, an acute inflammatory response to surgical trauma promotes the transfer of tumor cells to areas of the body remote from the lesion. For example, proinflammatory cytokines such as IL-1 and TNF-α stimulated the adhesion of circulating cancer cells [27]. However, it should be noted that acute inflammatory reactions after surgical trauma are often transient and do not lead to significant deterioration in oncological results.

In this regard, it is important to assess the content of pro- and anti-inflammatory cytokines in the blood. In the study, the increase in pro-inflammatory cytokines was significant on the next day after surgery, however, when using a preliminary carbohydrate load and dalargin, this phenomenon was less pronounced. This fact indicates that immune function was less suppressed under enkephalin conditions. This is also confirmed by the concentration of IFN-γ, which, with a moderate increase, is capable of exerting antitumor activity [9]. Despite a significant increase in IL-1β, IL-6, IL-8, there is a corresponding compensation by the high activity of anti-inflammatory IL-10.

Another important aspect reflecting the state of the immune system in the perioperative period is antitumor immunity. A marker of weakened antitumor, as well as antimicrobial immunity, is an increase in the level of IL-6 [18], which stimulates tumor growth by inhibiting apoptosis and inducing tumor angiogenesis.TNF-α has a largely similar tumorigenic effect [5,29]. Moreover, in addition to the direct effect on the formation of tumor tissue, TNF-α promotes the growth of blood vessels and the expression of adhesion molecules involved in the metastasis of transformed cells.Therefore, significantly low levels of these pro-inflammatory cytokines in the group using dalargin can be considered as a positive factor in protecting the body from the development of tumors.

It is known that overproduction of cytokines, including IL-1, IL-6 and TNF-α, plays a significant role in the prolongation of the hypermetabolic state [4,7]. An increase in the level of IL-6 also stimulates the production of antibodies, and a decrease in the formation of albumin and transferrin occurs. On this side, the increased concentration of these cytokines is one of the factors that slow down the recovery of patients in the postoperative period and increases the risk of infection.

Proinflammatory cytokines also increase the liver's production of CRP, which in turn is an inflammatory factor [22,28]. Therefore, a more significant decrease in the concentration of CRP in the blood of patients in the main group, according to the patterns of inflammation, should also be associated with a decrease in the activity of pathological processes.

Assessment of humoral immunity by determining the content of immunoglobulins showed that the immunological profile of patients in whom dalargin was present in the perioperative period was characterized by better indicators. Immunglobulins IgA and IgM in the control group tended to decrease on day 1 after surgery, which characterizes the state of immunity as suppression. In the main group, these antibodies remained without significant changes. A positive role of dalargin in increasing IgG by 7 days after surgery is also noted.

The study showed that the developed anesthesia method with the inclusion of enkephalin,was able to reduce immunosuppression and the activity of proinflammatory cytokines, which may create favorable preconditions for improving the oncological results of combined treatment of patients with malignant tumors of the oropharyngeal region.

Conclusion. The key role played by the immune system in the perioperative period highlights the importance of both reducing the morbidity of surgical interventions and finding new anesthetic agents aimed at reducing immunosuppressive effects. Support and moderate enhancement of the immune response in the perioperative period without dysregulation may potentially bring a number of benefits.

The results of this work can provide additional fundamental information on the use of enkephalin (dalargin) as a component of anesthesia. Its use in the perioperative period in patients with malignant neoplasms of the oropharyngeal region is associated with a lower concentration of pro-inflammatory interleukins, an increase in the concentration of IgG compared to endotracheal multicomponent anesthesia and may contribute to the activation of an antitumor immune response.

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