

Laser Irradiation of Blood as a Method of Prevention of Oral Mucositis

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Received: March 24, 2021; **Published:** March 29, 2021

Abstract

Purpose of the Study: Study the effectiveness of oral mucositis (OM) prevention by the stimulation of white cells phagocytic activity and activation of endogenous keratinocyte growth factor production by laser blood irradiation method (LBI).

Materials and Methods: The current study includes 470 children with malignant neoplasms receiving high-dose chemotherapy. All patients are divided into 3 groups, depending on the type of oral mucositis prevention. In group #1 of this study are included 220 children who were receiving the OM prevention with medication.

Group #2 of children is represented by 140 children. The OM prevention in this group was carried out by methods of local laser therapy. Laser radiation was applied to the areas of the oral cavity, where OM is most often developed.

The basis of this study are 110 patients of 3 groups, whom for the first time in the world prophylaxis of OM was carried out by laser irradiation of blood. 29 patients have already passed the high-dose polychemotherapy complicated by OM development. In the study we applied the method of identification of the white cells phagocytic activity state using the test sheet of latex microparticles. The study was performed before high-dose polychemotherapy, after LBI and after chemotherapy. Blood exposure to laser irradiation was made by placing the emitter on skin above the large vessels: areas of carotid arteries and veins, cubital, subclavian or popliteal.

Results: LBI technique was used in 260 courses of high-dose polychemotherapy. Stimulation of phagocytes by LBI method showed that application of this method before chemotherapy leads to the positive result in all cases. OM developed in only 1 child, which amounted to 0.9%.

Conclusion: Blood test for white cells phagocytic activity gives a chance to determine the actual readiness of the body to resist infections. If it was impossible to predict oral mucositis development before, now implementation of white cells phagocytic activity determination method improves the effectiveness of such prognosis. Thus, first in the world, all results that we obtained became possible only due to implementation of the white cells phagocytic activity test and stimulation of the white cells phagocytic activity and activation of the endogenous keratinocyte growth factor production by laser blood irradiation method.

Keywords: *Pediatric Oncology; Oral Mucositis; Laser Irradiation of Blood*

Introduction

Mucositis is a unifying term for erythematous and erosive-ulcerative lesions of the mucous membranes of the mouth, pharynx, esophagus and the whole gastrointestinal tract as a result of antitumor treatment [1]. Mucositis of the digestive tract are areas of damage to the mucous membrane, extending from the oral cavity to the anus [2]. Oral mucositis (OM) significantly reduces the quality of life of children, and in severe cases requires the introduction of narcotic analgesics and parenteral nutrition [3]. At the same time, experts from the United States argue that the costs of patients receiving anticancer therapy who developed OM are doubled in comparison with those patients who did not have this complication [4]. The reasons for such a rise in cost, first of all, should be attributed to interrupted treatment, leading to an extension of the length of stay of patients in the hospital, providing such patients with enteral nutrition and prescribing drug therapy, which is sometimes very expensive. These interruptions in treatment and a reduction in the dosage of chemotherapy drugs lead to a reduction in the survival rate of these patients [5].

In children, this pathology occurs more often. While in adults on the background of standard chemotherapy, the incidence of mucositis ranges from 10% to 50%, in children it ranges from 50% to 80% [6-8]. Most often, OM in children is associated with the use of high doses of methotrexate (HD MTX). It was also found that the frequency of severe cases of OM increases with the combination of HD MTX with other cytostatic drugs. All this makes the development of new methods of treating oral mucositis urgent. In recent decades, the world has continued an active search for means and methods of treating mucositis, however, standard treatment protocols have not yet been developed [9].

At the present time, it has been proven that infection is a secondary factor in the development of mucositis, and the fight against it is not the basis in treatment tactics. Scientists have found that even before the development of any clinical manifestations of mucositis, the first morphological changes are detected in the basal layer of the oral mucosa [12]. Children who have a high proliferative activity of basal cells are three times more likely to develop mucositis than the elderly [13]. Studies have shown that apoptosis of fibroblasts, endothelial cells, develops much earlier than the death of epithelial cells [14]. These studies revealed that endothelial cells produce keratinocyte growth factor (KGF) molecules. KGF is a trigger of growth and differentiation epithelial cells [15]. Direct diffusion of KGF from endothelial cells determines the normal development of the epithelial cover, respectively, the death of submucous endothelial cells stops the flow of physiological signals for the development of the epithelium and leads to its thinning and the formation of ulcers, on which colonies of pathogenic microorganisms or fungi settle. These findings pushed researchers towards a new approach to the treatment and prevention of OM. The International Association for Supportive Cancer Therapy (MASCC) and the European Society for Blood and Bone Marrow Transplantation (EBMT) have drawn up the Basic Oral Therapy Protocol. The Protocol also included recommendations on the use of palifermin for the prevention of OM. Palifermin (trade name Kepivance[®], manufactured by Biovitrum) is a non-glycated protein obtained from a genetically modified *E. coli* strain that contains a truncated version of the nucleotide sequence of keratinocyte growth factors [16].

One of the tasks facing the experts of this group was to assess the effectiveness of KGF in the treatment and prevention of OM in children. But the high cost of the drug and numerous side effects did not make it possible to use them in children's clinics [17]. Meanwhile, it has long been known that under the action of laser radiation, the proliferation of endothelial cells and pericytes is activated. Experimental and clinical studies indicate that low-intensity laser therapy (LILT), performed with low doses, leads to better results compared to the same therapy performed with high doses. Endothelial cells, participants in numerous vascular biological reactions (vasoconstriction, vasodilation, angiogenesis), were characterized by processes of increased proliferative activity and migration in response to laser radiation, including increased expression of keratinocyte growth factor and cytokines [14,15,19].

LILT can, at low doses, prevent cell apoptosis, enhance the proliferation of fibroblasts [18], keratinocytes [19], endothelial cells [20], and lymphocytes [21,22]. Researchers often observe a biphasic dose response, where low doses of laser radiation are much more effective in stimulating and repairing tissue than higher doses. Purpose. To investigate the effectiveness of prevention of oral mucositis by stimulating the phagocytic activity of leukocytes and activating the production of endogenous growth factor of keratinocytes, using laser blood irradiation (LBI).

Materials and Methods

The studies were carried out in compliance with the principle of voluntary informed consent. The present study included 470 children with malignant neoplasms receiving high-dose chemotherapy. All patients were divided into 3 groups, depending on the type of oral mucositis prophylaxis.

Group 1 of the present study included 220 children who received drug therapy in terms of prevention and treatment of OM, which included antifungal drugs, antibiotics, and rinsing with Miramistin. The overwhelming majority (82.2%) of children were with bone and soft tissue sarcomas and CNS tumors (Table 1).

Malignant neoplasms (n-220)	Sex distribution		%
	M (n-153)	F (n-67)	100%
Tumors of the central nervous system	39	11	50 - 22,7%
Osteosarcoma	33	12	45 - 20,5%
Ewing's sarcoma	32	15	47 - 21,4%
Soft tissue sarcomas	27	12	39 - 17,8%
Neuroblastoma	9	5	14 - 6,4%
Hepatoblastoma	5	4	9 - 4%
Nephroblastoma	5	4	9 - 4%
Others	3	4	7 - 3,2%

Table 1: A group of children who underwent OM prevention drug therapy.

The age of the patients ranged from 1.5 years to 17 years. The group "Others" is represented by two desmoplastic neoplasms. Three retinoblastomas, and two cases of germ cell tumors. Drugs in this group in the form of Fluconazole and Bisepitol, were prescribed when the leukocyte count was below 2000. When these children had low-grade fever, the leukocyte count was below 1000, drugs such as Cefepime, Meropenem were prescribed. By the end of chemotherapy, 53 children had developed OM, which was 24%. The second group of children at this stage of the study was represented by 140 children. In this group, prophylaxis of OM was carried out by methods of local laser therapy. Laser radiation was applied to the areas of the oral cavity, where OM most often develops.

The overwhelming majority (77.8%) of children were with bone and soft tissue sarcomas and CNS tumors (Table 2).

Malignant neoplasms (n-140)	Sex distribution		%
	M (n-85)	F (n-55)	100%
Tumors of the central nervous system	26	18	44 - 31,4%
Ewing's sarcoma	14	9	23 - 16,4%
Osteosarcoma	13	8	21 - 15 %
Sarcomas of soft tissues	15	6	21 - 15 %
Neuroblastoma	8	5	13 - 9,3%
Hepatoblastoma	3	2	5 - 3,6%
Nephroblastoma	4	3	7 - 5%
Others	2	4	6 - 4,3%

Table 2: A group of children who underwent OM prevention local laser therapy.

The age of the patients ranged from 1 to 16 years. The group “Others” included four retinoblastomas and two germ cell tumors. When carrying out preventive measures, the areas of possible localization of OM were exposed to laser irradiation. These are the cheeks, the hyoid region and on the projection area of the tonsils. In this group of children, OM developed in 19 patients, which amounted to 13.6%. Prior to that, in early 2017, we conducted a study comparing the effectiveness of drug decontamination for the prevention of OM and laser therapy. In the group (n-13), who underwent drug decontamination, OM developed in 5 patients (35%). In the second group (n-14), local laser therapy was performed percutaneously for 2 minutes on the cheek and chin area 3 - 4 days before the start of chemotherapy. The sessions were held 2 times a day. Oral mucositis developed only in 2 out of 14 children, which was 14%. OM of the 1st degree developed in a child with a germ cell tumor of the ovary, OM of the 2nd degree in a child with Ewing’s sarcoma.

For the first time, based on the fact that an increase in the phagocytic activity of leukocytes in LBI can prevent the rapid development of pathogenic microflora, even with the development of leukopenia [3], we decided to conduct LBI in patients before chemotherapy sessions.

The method of influencing the blood of LI was developed at the Novosibirsk Research Institute of Circulatory Pathology under the leadership of Academician Meshalkin E.N. in 1980 This procedure is carried out intravenously or by placing a radiator over large vessels and has become known as transcutaneous laser blood irradiation or abbreviated as “ TLBI “. Numerous studies have shown that the effectiveness of intravenous and supravenuous laser exposure to blood is practically the same [23]. The mechanism of the therapeutic action of laser hemotherapy (LHT) is common in various pathologies. The results, confirmed by hundreds of studies, prove the truth of the assumption that LBI refers to immunomodulatory techniques. Researchers [24-33] identified the secondary effects of laser hemotherapy, leading to the following pronounced therapeutic effects:

- Reduction or disappearance of ischemia in organ tissues: cardiac output increases, total peripheral resistance decreases, coronary vessels expand, exercise tolerance increases.
- Normalization of energy metabolism of cells subjected to hypoxia or ischemia, maintenance of cellular homeostasis.
- Anti-inflammatory effect due to inhibition of the release of histamine and other mediators of inflammation from mast cells, inhibition of prostaglandin synthesis, normalization of capillary permeability, reduction of edema and pain syndromes;
- A positive effect on the processes of lipid peroxidation in blood serum;
- Normalization of lipid metabolism. Let us consider in more detail how and how laser hemotherapy (LHT) affects the body of patients.

Experimental and clinical studies have proved that LILI normalizes microcirculation: it activates the work of myocytes and endotheliocytes, stimulates the functional activity of blood vessels by dilating them and opening reserve capillaries. Improvement of microcirculation leads to accelerated elimination of toxins from the body (detoxification), increased oxygen delivery to tissues and organs (anti-ischemic effect). At the same time, cardiac output increases, coronary vessels expand, and exercise tolerance increases. The release of heparin by mast cells leads to blood thinning, which improves the blood supply to tissues and organs, especially in the microvascular bed. Considering these properties of LBI (stimulation of phagocytic activity and activation of endothelial cells), we decided to apply this technique for the prevention of OM.

The study of the phagocytic activity of leukocytes is the most important factor in determining the nonspecific resistance of the organism. In our study, to determine the state of phagocytic activity of leukocytes, we used a technique with a test object of latex microparticles. In our study, we used particles with a diameter of 1.7 μm [2]. The method for determining the phagocytic activity of leukocytes is as fol-

lows. Heparinized (50 U/ml) blood in an amount of 0.5 ml is incubated in conical test tubes at 37°C with 0.05 ml of washed latex suspension. After 5 minutes and after 1 hour, smears are prepared, which are stained according to Romanovsky - Giemsa. Then the phagocytic index (PhI) was calculated - the percentage of phagocytic cells out of 100 phagocytic cells and the phagocytic number (PhN) - the average number of particles captured by one cell. The disadvantages of the method include the impossibility of determining the completeness of phagocytosis, because latex particles are not digested. The present study included 110 children with malignant neoplasms (Table 3).

Malignant Neoplasms (n-110)	Sex distribution	
	M (n- 68)	F (n- 42)
Tumors of the central nervous system	36	18
Osteosarcoma	14	10
Ewing's sarcoma	7	4
Rhabdomyosarcoma	4	3
Neuroblastoma	1	1
Nephroblastoma	1	2
Others	5	4

Table 3: Patients for whom the prevention of OM was carried out by the method laser blood irradiation.

The group “Other” included patients: retinoblastoma - 1, fibrosarcoma - 1, chondrosarcoma - 1, angiogenic sarcoma - 1, desmoplastic tumor - 1, germinoma - 1, mesenchymal tumor - 1, kidney sarcoma - 1, ovarian sarcoma - 1.

29 patients, before the use of LBI, had already undergone high-dose polychemotherapy, which was complicated by the development of OM. All patients underwent LBI 1-2-3 days before the start of chemotherapy. Laser devices: In our study, we used the MR4 Super Pulsed Laser magneto-infrared laser therapeutic apparatus made by Multi Radiance Medical, the USA based manufacturer.



Figure

The effect of laser radiation on the blood was carried out by imposing an emitter on the skin over large vessels: zones of the carotid arteries and veins, cubital, subclavian or popliteal. The application is stationary, the exposure time percutaneously on large vessels is from

10 to 15 minutes with two emitters. The dose of laser radiation in 1 minute was 0.006 J/cm². The total dose per session is 0.18J, with a light spot area of 4 cm², the total dose per session is 0.045 J/cm². The total exposure time of the session is from 10 to 20 - 30 minutes, depending on the child’s age (blood volume). The time is indicated as total, i.e. irradiation with two emitters for 5 minutes is 10 minutes. 30 minutes, this is irradiation with 2 emitters for 15 minutes. The number of sessions depends on the parameters of PhI and PhN before laser blood irradiation and can range from 1 to 3 sessions.

Clinical Example

Girl M. 7 years old. Dz: Osteosarcoma of the right femur. T2N0M0. Stage IIB. Condition after combined treatment. Clinical group II. He is undergoing treatment at the Scientific and Research Center, where, for health reasons, he received antitumor treatment. Polychemotherapy according to the OS-2006 protocol was started on 06.12.17. The second course was held from 15.01 to 22.01.18. During the first two courses of PCT, the child, even against the background of medical decontamination, developed OM of the 1st degree. During the third course of chemotherapy, including high doses of methotrexate, it was decided to conduct LGT and analyze the dynamics of phagocytic activity after 3 20 minutes of laser hemotherapy sessions. The 3rd course was conducted from 02.02.2018 to 23.02.2018 according to the OS-2006 protocol: - Methotrexate 12 g/m² 1, 8 days IV cap for 4 hours, RD = 8 g, SD = 8 g; - Cisplatin 50 mg/m² 15, 16 days intravenous cap for 24 hours, RD = 35 mg, SD = 70 mg; - Doxorubicin 45 mg/m² 17, 18 days intravenous cap for 24 hours, RD = 31.5 mg, SD = 63 mg. Table 4 Study of the dynamics of the phagocytic activity of leukocytes in the child M.

Patient	Number of LHT sessions	Time of phagocytic activity study	Time of incubation			
			5'		60'	
			PhI	PhN	PhI	PhN
M., 7 years	3	Before laser therapy	12%	3,2	53%	7
	By 20'	'After 3 sessions of LGT	20%	5,4	72%	8,3
		On the 8 th day after LGT	74%	8,1	71%	10,1
		On Day 14	48%	8	64%	12,4
		On day 18	60%	7,2	86%	19
		On the 27 th day	72%	5,8	82%	15,5

Table 4

The girl endured the treatment satisfactorily. The child did not develop oral mucositis. It is noted that even 5 days after the end of high-dose chemotherapy, the child retains high phagocytic activity. Compared to the phagocytic activity before LGT, it increased more than 3 times. High phagocytic activity was also noted 4 weeks after LHT. The effectiveness of phagocytic activity after LBI was tested by the method of bacteriological inoculation of microflora from the oral cavity. Crops of microflora from the oral cavity were taken before the patients of the 3rd group LBI. Repeatedly these crops were taken on the 2nd day after LBI. A total of 34 microbiological studies were carried out using the Bact/ALERT® FA media (France) for aerobic and anaerobic flora. Analysis of the effectiveness of LBI on pathogenic microflora of the oral cavity showed its high efficiency. In 100% of cases, after LBI, the pathogenic flora was not sown.

Results and Discussion

Such stimulation of phagocytes by the method of laser irradiation of blood showed that carrying out this technique before the start of chemotherapy, in all cases, leads to a positive result. Only one child developed OM, which was 0.9%. The results obtained gave rise to filing a patent application “Method for the prevention and treatment of oral mucositis in children”, which was received on June 24, 2019 (RU

2692448). The number of conducted stimulating sessions of the LBI, first of all, depends on the initial indicator of the phagocytic activity of leukocytes. At high rates, the number of stimulating sessions can be limited to 1-2 sessions. And, conversely, with low initial indicators of phagocytic activity, the number of sessions carried out once a day can be increased to 3. The total session time depends on age. For children under 2 years old, it was 10 minutes, up to 10 years old, it was 20 minutes, for older children 30 minutes. We have noted for the first time a high phagocytic activity of platelets. The fact that a platelet can act as a true phagocyte was determined by American scientists in 1976 [32]. They also suggested that the phagocytic process is similar to that characteristic of polymorphonuclear leukocytes. We, in turn, discovered for the first time that LBI sharply stimulates the phagocytic activity of platelets (Figure 1).

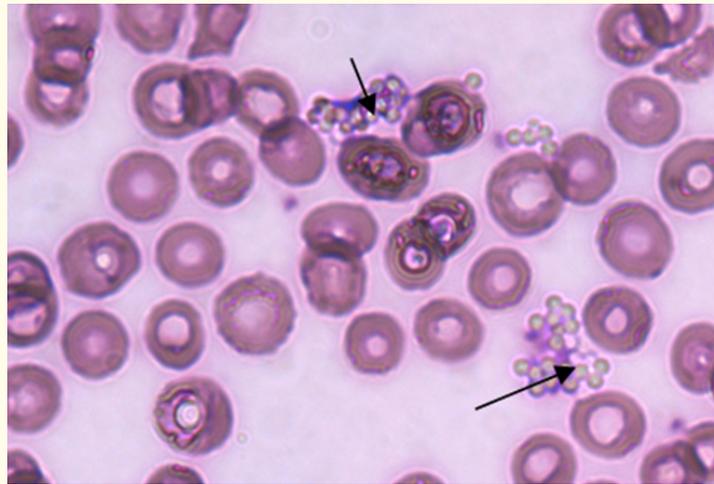


Figure 1: Phagocytosis by platelets after LBI.

As already mentioned, the cytotoxic effect of chemotherapy or radiation therapy kills not only tumor cells, but also rapidly dividing normal cells, in our case, these are epithelial cells. The death of these cells leads to thinning of tissues, in particular of the cheeks. In our study, we measured the thickness of the cheeks before the start of chemotherapy and laser irradiation of the blood, and then after the course of high-dose polychemotherapy. An ultrasound measurement of the thickness of the cheek tissue showed that the measurements before and after chemotherapy remained the same. This is an indirect confirmation of the fact that LBI actually activates myocytes and endotheliocytes protecting them from the cytotoxic effect of chemotherapy drugs [29]. To assess the effectiveness of prophylactic laser hemotherapy (LHT) sessions, we also used color Doppler ultrasound imaging (DUI) of the cheek vessels before and after and the LBI. This method is the fastest and most painless way to check for vascular changes during LHT. Domestic studies have proven that laser blood irradiation leads to the normalization of microcirculation. LBI stimulates macrophages to release nitric oxide (NO). The long-term vasodilation effect of NO contributes to improved nutrient delivery. LBI activates the work of myocytes and endotheliocytes, producing keratinocyte growth factor, and direct diffusion of KGF from endothelial cells determines the normal development of the epithelial cover of the oral mucosa.

These studies have shown that after the LBI, vasodilation in the studied area is noted, and microcirculation improves. And also an increase in the pulsation index, which reflects the elastic-elastic properties of the arteries. That testifies to the effectiveness of the LBI carried out with the aim of preventing OM. To assess the effectiveness of laser irradiation of blood, we also used laser Doppler fluometry

(LDF). Laser Doppler flowmetry is successfully used in the diagnosis of microcirculatory changes in capillary blood flow in cancer of the skin, in the assessment of microhemodynamics, and in the assessment of the effectiveness of therapy. In our case, this is laser blood irradiation. The main indication for the use of LDF is the need to assess the systemic state of microcirculation in patients with lesions of the oral mucosa. The use of LDF makes it possible to assess the state and disorders of blood microcirculation and, thereby, to exercise objective control over the effectiveness of laser hemotherapy.

The LDF method is based on optical non-invasive sensing of tissues with laser radiation and analysis of radiation scattered and reflected from erythrocytes moving in tissues. The magnitude of the increase in vascular diameters is associated with the functioning of endothelial cells. An increase in the synthesis of nitric oxide (NO) leads to an increase in the diameter of the vessels. When endothelial cell function is impaired, the ability to produce nitric oxide and other compounds is reduced. In our study, endothelial dysfunction occurs during high-dose chemotherapy. When conducting laser irradiation of blood, the synthesis of NO increases, which is evidence of the stimulation of endothelial cells. Research methodology. The device's sensor is attached to the cheek with an adhesive plaster (Figure 2). After that, readings are take.



Figure 2: Laser doppler flowmetry in patient B.

As a result of registration of LDF-grams of patient B. and its subsequent processing, the data shown in graph 1 were obtained.

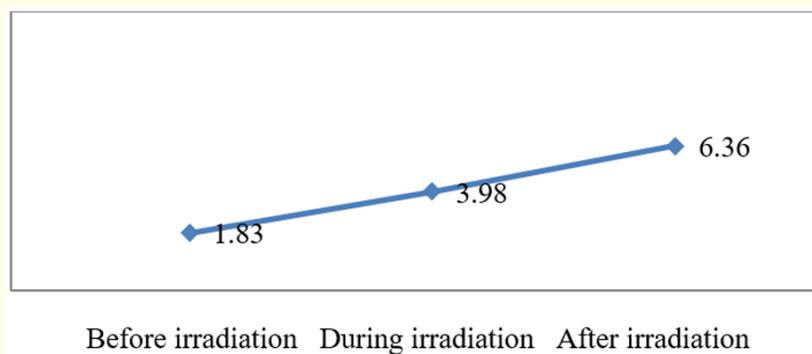


Figure 3: The arithmetic mean of the microcirculation index.

These changes in the study are characteristic of a pronounced increase in perfusion of the hyperemic type, characterized by increased blood flow into the microvasculature, activation of anastomoses, a significant increase in the number of functioning capillaries, expansion of microvessels, and improved regulation of vascular tone. The results of laser Doppler fluometry may indicate the effectiveness of LBI performed to stimulate endothelial cells that produce keratinocyte growth factor. Summing up the results of this study, it should be noted that: despite the simplicity of the LBI technique, its high efficiency, when performing the LBI, it is necessary to know the main contraindications. These are general contraindications for laser therapy and taking into account the principles of operation of this technique, special attention should be paid to: acute bleeding, epilepsy, thyrotoxicosis, deep vein thrombosis, blood diseases (hemophilia, Verlhof's disease, etc.) and severe thrombocytopenia. Thrombocytopenia is common in patients receiving chemotherapy. Given the fact that with LBI, mast cells secrete endogenous heparin, bleeding is possible in such patients. Most often these are nosebleeds.

Conclusion

The introduction of the LBI technique into oncological practice will help improve the quality of treatment for children with cancer, increase survival and significantly reduce costs.

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Volume 4 Issue 4 April 2021

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