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RESEARCH ARTICLE

EFFICACY OF LAETRILE IN TREATMENT OF CANCER PATIENTS WITH CHEMORADIATION ORAL MUCOSITIS

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ABSTRACT

Background: Post-chemoradiation mucositis is a common and serious side effect that occurs in patients undergoing cancer treatment. It is an inflammatory condition of the mucous membrane that can cause significant discomfort, pain, and a significant reduction in quality of life. Among the many methods used to relieve and treat mucositis, the drug Laetrile has attracted particular attention due to its potential therapeutic properties.

The aim of this study was to evaluate the effectiveness of Laetrile in treating post-chemoradiation mucositis.

Materials and Methods;The study involved 89 patients diagnosed with cancer of the oral mucosa (C00-C06, C10, C13, C14 according to ICD-10) stages II and III (T2-3, N0-1, M0), aged 55 to 67 years, who received chemoradiation therapy to the head and neck area. Depending on the treatment method, patients were divided into two groups: comparison traditional treatment) and the main (developed method that reduced the incidence of bleeding gums, erosions and ulcers of the oral mucosa.

Results: The use of Laetrile allowed to achieve a therapeutic-prophylactic effect in 55 (93.2%) of 89 patients treated with Laetrile while in the comparison group (traditional treatment) in 19 (63.3%) of 30 patients

Conclusion: Laetrile is an interesting alternative in the treatment of postchemoradiation mucositis thanks to its potential ability to reduce inflammation and promote tissue regeneration. Thus, although Laetrile is a promising option for managing the symptoms of mucositis, its potential benefits and risks have yet to be clarified in further research.

Keywords: oral mucositis, treatment, rehabilitation

INTRODUCTION

Head and neck tumors represent a significant group of malignant neoplasms, characterized by a gradual increase in incidence[1]. Despite the progress in the field of early diagnosis and treatment of oncological diseases, complex antitumor treatment using chemotherapy and radiotherapy is inevitably accompanied by changes in the surrounding normal tissues (destructive, erosive-ulcerative and necrotic changes[2-4].

Currently, chemotherapy remains one of the most common treatment methods, despite the progress made in recent years in the management of oral and maxillofacial (OMF) cancer[5-7].

It is used either alone or in combination with other therapeutic methods, preventing the proliferation of atypical cancer cells. The oral cavity is very vulnerable to the direct and indirect toxic effects of chemotherapy, which is due to the lack of selectivity of the targeted cells, as a result of which both tumor cells and normal cells are damaged. This is due to the specific features of the oral cavity, which include a high level of turnover of mucosal cells, the presence of a complex and diverse microflora in the oral cavity, as well as minor traumatic injuries resulting from the implementation of normal oral functions (chewing, swallowing, vocalization).

Mucositis is one of the most common side effects of antitumor therapy, significantly reducing the quality of life of cancer patients[8-10].

Oral mucositis generally begins 5-10 days following the initiation of chemotherapy and duration depends on the type, dose, and course of treatment[11,12].

On average, the incidence of mucositis is 29–66% the most severe complications develop in patients receiving high-dose radiation therapy for head and neck cancer[13].

The development of mucositis leads to interruptions in courses of antitumor treatment and, as a consequence, a decrease in its effectiveness, which negatively affects the prognosis of the disease[13-15].

Pathogenesis of radiation-chemotherapy mucositis the following five-stage model [16] , is based on the evidence available to date (figure 1).

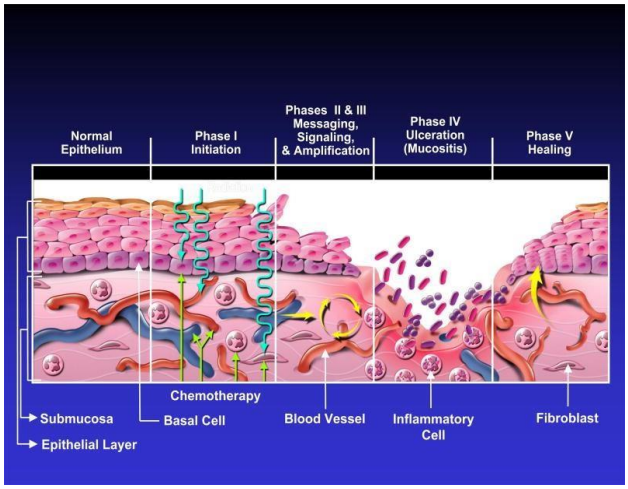

Figure 1. Current five-phase pathobiologic model of oral mucositis. (Reprinted from Sonis ST. A Biological Approach to Mucositis. J Support Oncol 2004; 2:21–36).

The degree and extent of oral mucositis that develops in any particular patient and site appears to depend on factors such as age, gender, underlying systemic disease and race as well as tissue specific factors (e.g. epithelial types, local microbial environment and function)[17].

A wide variety of scales have been used to record the extent and severity of oral mucositis in clinical practice and research. The World Health Organization (WHO) scale combines both subjective and objective measures of oral mucositis.

Mucositis is graded using the World Health Organization (WHO) Mucosal Injury Scale[17](Table 1).

Table 1.

World Health Organization (WHO) scale for oral mucositis

Grade 0 = No oral mucositis
Grade 1 = Erythema and Soreness
Grade 2 = Ulcers, able to eat solids
Grade 3 = Ulcers, requires liquid diet (due to mucositis)
Grade 4 = Ulcers, alimentation not possible (due to mucositis)

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 includes separate subjective and objective scales for mucositis [18].

National Cancer Institute (NCI) Oral Mucosal Injury Scale (Table 2).

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0

Oral mucositis (clinical exam)
Grade 1 = Erythema of the mucosa
Grade 2 = Patchy ulcerations or pseudomembranes
Grade 3 = Confluent ulcerations or pseudomembranes; bleeding with minor trauma
Grade 4 = Tissue necrosis; significant spontaneous bleeding; life-threatening consequences
Grade 5 = Death
Oral mucositis (functional/symptomatic)
Grade 1 = Minimal symptoms, normal diet
Grade 2 = Symptomatic but can eat and swallow modified diet
Grade 3 = Symptomatic and unable to adequately aliment or hydrate orally
Grade 4 = Symptoms associated with life-threatening consequences
Grade 5 = Death

The WHO Mucosal Injury Scale is the most commonly used scale in clinical and research settings, while the NCI CTCAE scale is often used as a measure of overall toxicity.

Signs and symptoms of mucositis include:

-Red, shiny, or swollen mouth and gums;

-Blood in the mouth;

-Sores in the mouth or on the gums or tongue;

-Soreness or pain in the mouth or throat;

-Difficulty swallowing or talking;

-Feeling of dryness, mild burning, or pain when eating food;

-Soft, whitish patches or pus in the mouth or on the tongue;

-Increased mucus or thicker saliva in the mouth.

Oral mucositis can:

-Cause pain;

-Restrict oral intake;

-Act as a portal of entry for organisms;

-Contribute to interruption of therapy;

-Increase the use of antibiotics and narcotics.

In addition, mucositis significantly increases the cost of treating cancer patients and increases the duration of hospitalization. In this regard, there is a need to search for and develop.

The main clinical signs of mucositis include: oral pain of varying intensity, dry mouth, inability to eat. To reduce the severity of mucositis caused by chemo- and / or radiation therapy, it is proposed to develop multidisciplinary guidelines for oral care, familiarize staff and patients with them.

Oral Care: Standardized oral care protocols are recommended to prevent oral mucositis in all age groups and across all cancer treatment modalities (LOE III).
Mucositis Study Group of the Multinational Association for Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) has developed clinical practice guidelines for the management of mucositis[19-21]. Management of oral mucositis is divided into the following sections: nutritional support, pain control, oral decontamination, palliation of dry mouth, management of oral bleeding and therapeutic interventions for oral mucositis.

Good oral care regimen can help prevent or decrease the severity of mucositis and, just as important, help prevent the development of infection through open mouth sores. The mainstay of an effective oral care regimen is mouth rinses,Such recommendations should include mechanical cleaning (brushing teeth with a soft brush, dental floss), rinsing the mouth to reduce the accumulation of bacteria (soft rinses), and moisturizing and lubrication (applying moisturizers) to the surface of the oral mucosa. In the presence of minor pain in the mouth, treatment should begin with rinsing. If they are insufficiently effective, local anesthetics are added (for example, 2% lidocaine solution). In the presence of extensive painful ulcers, systemic analgesics are added to the treatment.

Currently, various drugs are recommended for the treatment of inflammation of the mucous membranes, including herbal ones[22-23].

Use of natural medicinal herbs for the treatment of complications and side effects Cancer therapy gained strength in the last few decades and became a new area researches. In the context of symptoms in the treatment of radio-induced mucositis, the effectiveness of chamomile, aloe vera, honey extract is currently being studied, Manuka, vitamin A, glutamine[25-26].

Among the variety of methods used to relieve and treat mucositis, the Laetrile attracts special attention due to its potential therapeutic properties[27].

Laetrile is a cyanogenic glycoside, also known as vitamin B17, is a derivative of amygdalin, a compound found in the seeds of fruits such as apricots, peaches, and almonds. Laetrile has been used in the past as an alternative cancer treatment, but its effectiveness in the fight against cancer remains controversial[28]. However, interest in its use in the treatment of post-chemoradiation mucositis has increased, as the compound may have the ability to reduce inflammation and stimulate tissue regeneration..In the 1950s, an intravenous form of amygdalin was patented and named laetrile, a semisynthetic compound composed of D-glucuronic acid and mandelonitrile.

One possible mechanism of action of Laetrile is its ability to stimulate apoptosis of damaged cells, which may speed up the healing process of the mucosa[29-31]. In addition, some studies point to its role in modulating the immune response and reducing inflammation, which may also be useful in mucositis[32,33].

The aim of this study was to evaluate the effectiveness of Laetrile in treating post-chemoradiation mucositis.

MATERIAL AND METHODS

The clinical study was conducted at the State Budgetary Healthcare Institution of the Republic of Crimea"Crimean Republican Oncology Clinical Dispensary named after V. M. Efetov". The study included 89 patients diagnosed with cancer of the

cervical spine (C00-C06, C10, C13, C14 according to ICD-10) stages II and III (T2-3, N0-1, M0), aged 55 to 67 years (the average age was 63.6±4.35 years), of which 69 were men (77.53%), 20 were women (22.47%), who received chemoradiation therapy to the head and neck area. Antitumor treatment was performed by an oncologist according to clinical recommendations according to the scheme: single focal dose (SFD) from 1.8 to 2 Gy, total focal dose (TFD) from 40 to 60 Gy using the gamma installation of the linear apparatus Elekta Compact TM, Versa HD [2]. Chemotherapy with cisplatin at 100 mg/m2 intravenously at a rate of no more than 1 mg/min with pre- and posthydration every 3 weeks (on the 1st, 22nd and 43rd days during RT) and carboplatin at 1.5-2.0 AUC (during RT).

During the initial examination of the patient, complaints were clarified in a conversation, and a detailed anamnesis of the disease and life was collected. In this case, much attention was paid to identifying premorbid factors as predictors of the disease, namely: the presence and duration of bad habits, occupational hazards, a burdened family history, comorbid pathology.

During the initial examination of the skin of the face and neck, special attention was paid to changes in color and contours. Examination of the organs and tissues of the oral cavity was carried out according to WHO recommendations (1997), determining the condition of the dentition, periodontium, the presence and volume of dental plaque. Of particular interest was the study of the oral mucosa: color, relief, moisture, hyperemia, swelling, the presence of elements of damage - papules, erosions, aphthae, ulcers, scars, etc. Mucositis was diagnosed according to the WHO classification (1979). The study included patients only with grades III (erythema and ulcers, inability to swallow solid food) and IV (ulcers and food intake impossible) mucositis.

Depending on the treatment method, patients were divided into two groups: the main group (59 patients: 44 men, 15 women) and the comparison group (30 people: 25 men, 5 women). In the main group, oral cavity sanitation was performed - professional oral hygiene, tooth extraction and filling of carious cavities, the use of soft toothbrushes and Mexidol-phyto toothpaste, which restores microcirculation, activates local immunity, has an anti-edematous effect, reduces bleeding, stimulates wound healing, including purulent ones, has an anti-inflammatory, metabolic, immunocorrective effect. Antiseptic treatment was performed with a 0.005% chlorhexidine solution and rinsing with Laetrile (15 drops per glass (200 ml) of water) 2 times a day for 2 weeks. The oral mucosa was anesthetized in the presence of ulcers and erosions before or after chemoradiotherapy by applying Desensetinan gel for 5-7 minutes, then washing it off with water; a collagen patch Suprasorb (natural collagen dressing (4X6X0.8 cm, 5 pieces) moistened with a solution (drops) of Laetrile B-17, which regulates the functioning of the cell membrane, removes oxidation products from the body, has an antiseptic and analgesic effect, was applied to the affected areas of the oral mucosa. The patients in the comparison group received traditional treatment - antiseptic treatment with 0.06% chlorhexidine solution and olive oil applications. Observation periods: before, on the 3rd, 5th and 7th days of observation.

RESULTS

During the initial visit, the main complaints of patients were general weakness, headache, increased nervous excitability, sore throat, thickening of saliva, severe dry mouth (hyposalivation), pain when eating and bleeding gums, tooth mobility and exposed necks, inability to eat solid food, loss of shine and redness of the oral mucosa and lips, burning and tingling sensations, plaque on the teeth and oral mucosa, the presence of "ulcers" that are painful to palpation, taste disturbances, and bad breath. Most of the examined patients were diagnosed with oral mucositis of the third degree of severity: with MN stage II - in 17.97% of cases, with MN stage III - in 48.0%. Mucositis of the fourth degree, respectively, in 12.35% and 21.34% of cases. Early manifestations of mucositis and objective symptoms in patients were characterized by hyperemia and swelling of the oral mucosa, bleeding gums, the presence of erosions covered with fibrinous plaque, painful on palpation, focal or confluent epitheliitis, erosive and ulcerative-necrotic processes in 72-84% of patients.

Most often (in 82-100% of cases), continued development of mucosal edema, isolated small-focal erosions, less often - confluent large-focal erosions, and bleeding gums were observed. In 30-55% of patients, focal or confluent epitheliitis, erosions and ulcers were detected. The absence of filiform papillae on the dorsal surface of the tongue ("varnished tongue") was detected. In 8 (8.9%) patients, mucositis was complicated by pseudomembranous candidiasis: a characteristic abundant cheesy coating on the tongue was determined.

Hemorrhagic manifestations in the main group appeared 2-3 times less often than in the control group. At the same time, erosions, ulcers, necrosis and confluent epitheliitis did not occur in any of the patients treated with Laetrile. During chemotherapy, 92% of patients, when describing saliva, called it “tasteless”,

"thick", tried to swallow, but did not swallow because of its "viscousness", spit or kept their mouths slightly open so that saliva flowed onto a napkin or into a container, for which they were forced to lie face down on the bed. 8% of patients did not complain.

The dynamics of rheological parameters of the oral fluid of patients in both groups during treatment are presented in Table 3.

Table 3. Dynamics of rheological parameters of oral fluid of patients in the main group and comparison group.

Indicator	Main group (n=59)		Comparison group (n=30)	
	Before treatment	After treatment	Before treatment	After treatment
Volume of oral fluid (ml)	0,14±0,04	0,43±0,14*	0,15±0,05	0,17±0,07
Rate of salivation (ml/min)	0,4±0,11	1,3±0,51*	0,4±0,10	0,5±0,12
Viscosity of oral fluid (relative units)	7,4±1,90	2,5±1,03*	6,8±1,98	6,3±2,33

*Note: * - reliability of differences in the parameters (p<0.05) in the main group compared to the comparison group.*

The salivation rate parameters in individuals receiving Laetrile tended to increase statistically significantly, in some cases approaching similar parameters in healthy patients. When using complex therapy with Laetrile, the salivation rate was significantly higher compared to the parameters obtained during chemoradiation therapy in the comparison group (with classical (traditional) therapy), while the salivation rate parameters in episodes complicated and not complicated by mucositis did not differ statistically.

The salivation rate in patients in the comparison group during treatment is shown in Fig. 2, and in the main group - in Fig. 3.

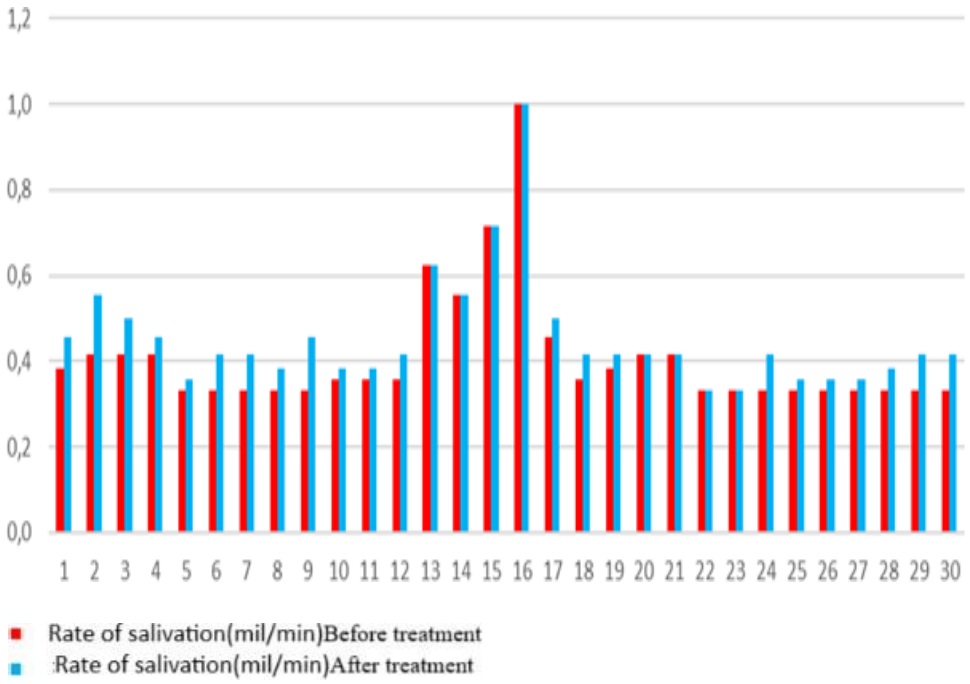

Figure 2. Rate of salivation in patients **(n=30)** of the comparison group during treatment

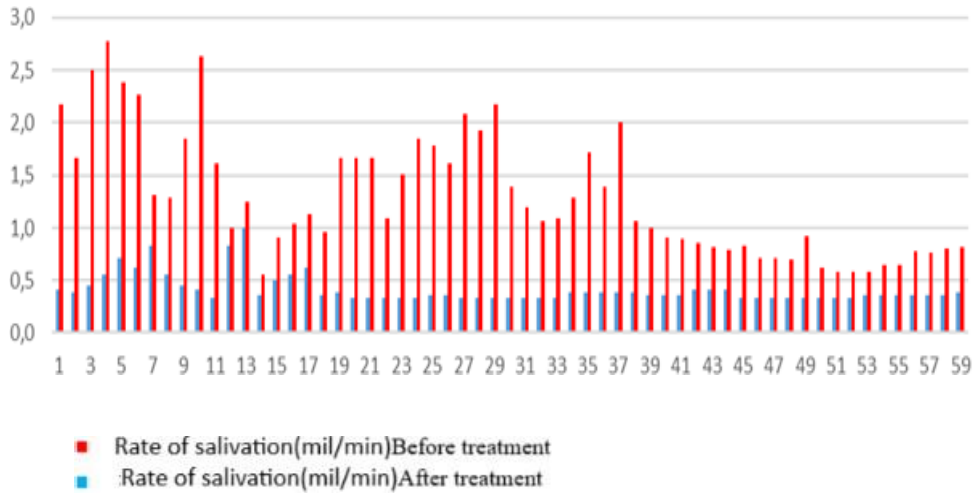

Figure 3. Rate of salivation in patients **(n=59)** of the main group during treatment

At the second stage of the study, the administration of Laetrile increased the volume of oral fluid in patients in the main group to 0.43±0.14 ml compared to the comparison group with standard therapy, where this figure was 0.17±0.07 ml ($p < 0.05$). There were no complaints from patients about the side effects of Laetrile during the use of Laetrile. From the data presented in Table 5.1, it is evident that when taking Laetrile, the individual indicators of saliva viscosity of patients were significantly lower (6.3±2.33 and 2.5±1.03), and the indicators of the rate of salivation were higher than those in the comparison group (1.3±0.51 and 0.5±0.12). Improvement of salivation characteristics had a positive effect on the well-being and behavior of cancer patients, since the quality and quantity of saliva did not interfere with its automatic swallowing, which confirms that the administration of Laetrile significantly improves the quality of life of cancer patients during chemotherapy and radiation therapy. Saliva viscosity in the comparison group significantly exceeds this indicator in the main group (according to median indicators, more than twice: 6.1 and 2.3, respectively; $p < 0.05$).

Figure 4 and figure 5 show the data on the viscosity of oral fluid in patients of the main group during treatment and the comparison group.

We provide diagrams with individual data for all patients to demonstrate the level of variability of their personal indicators of oral fluid rheology. With statistical significance of these parameters, there are cases that go beyond the average variation series, which is apparently associated with both the morphofunctional features of the salivary glands (primarily the parotid gland) and the features of the autonomic regulation of salivation. This is especially demonstrative in the comparison group and may be important for the doctor's work in assessing the effectiveness of therapy.

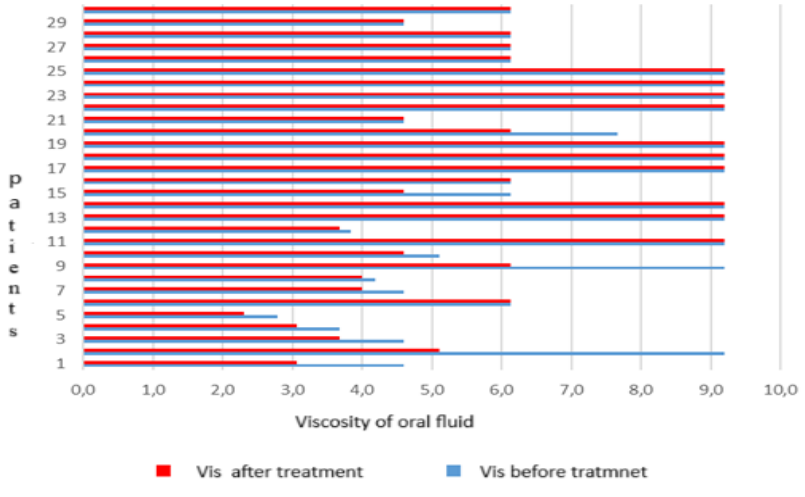

Figure 4. Viscosity of saliva in patients of the comparison group during treatment

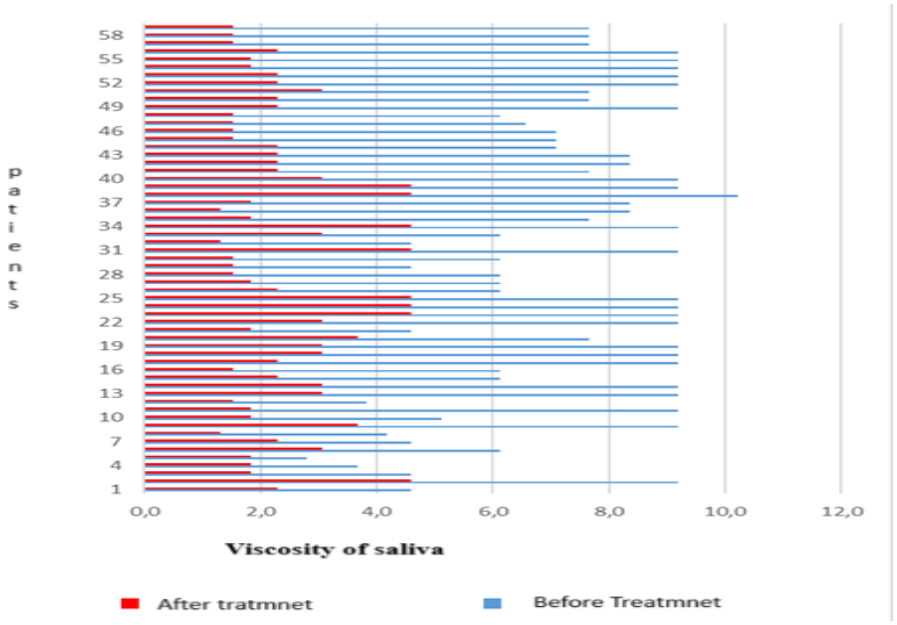

Figure 5. Viscosity of saliva in patients of the main group during treatment

The pH value after treatment shifted to the right, i.e. to an acidic environment in more than half of the comparison group and more than a third of the patients in the main group. The acid-base balance shifted to the left, i.e. to an alkaline reaction in less than a third of the patients in the comparison group and in a fifth of the patients in the main group (Tables 4 and 5).

Table 4. Acid-base balance in patients in the control group

Patients (n=30) of the comparison group			
After treatment		pH range	
Quantity	%		
8	26,67	>7,5	Alkaline
6	20,00	6,8- 7,4	Norm
16	53,33	<6,7	Acidity

Table 5. Acid-base balance in patients of the control group

Patients (n=59) of the **control group**			
After treatment		pH диапазон	
Кол-во	%		
12	20,34	>7,5	Alkaline
27	45,76	6,8- 7,4	Norm
20	33,90	<6,7	Acidity

Thus, the obtained data allow us to conclude that the acid-base balance in patients of the main group in the pH range of "normal" is 45.76%, which is significantly (2.3 times) higher than in the comparison group. Accordingly, in the main group, a decrease in the acidity level of the percentage component among patients is observed 1.6 times less often, in contrast to the comparison group.

Thus, in patients suffering from mucositis against the background of oral cancer, clinically significant changes in salivation parameters are associated with the aggressiveness of chemoradiation therapy. Complex mechanisms of regulation of salivation and its disorders require further research. The features of salivation dysfunction in cancer patients receiving chemoradiation therapy of the oral cavity are a decrease in the volume and rate of salivation, as well as an increase in the viscosity of oral fluid. The use of Laetrile for 10-14 days from the beginning of the course of chemoradiation therapy can significantly prevent a decrease in the volume and an increase in the viscosity of saliva and minimize the associated decrease in quality of life.

To assess the local mechanisms of regulation of immune reactions in patients with mucositis, the content of pro- and anti-inflammatory interleukins was determined in the oral fluid.

The concentration of pro-inflammatory IL-1b in the saliva of patients before the start of cancer treatment - chemoradiation therapy - was 126.14 ± 45.01 pg / ml. The relatively low concentration of anti-inflammatory IL-10 at this time was 94.96 ± 44.20 pg / ml. During this period, dental sanitizing treatment measures were carried out. During the main complex of cancer therapy, mucositis developed, which required local therapy. The concentration of IL-1b at this point in the patients' saliva averaged 303.99±130.18 pg/ml (an increase of almost two times), and IL-10 - 31.68±5.91 pg/ml (a decrease of 50%).

The developed mucositis required local treatment. After the start of local therapy, we took saliva samples at intervals of 1 day.

When using classical therapy, we did not obtain statistically significant differences on days 1 through 7, the fluctuations in values were less than 15–20%, which did not allow us to consider the results significant with such variability.

When using Laetrile to level out inflammation in oral post-radiation mucositis, the concentration of pro- and anti-inflammatory cytokines changes differently. During the first day, the IL-1b concentration decreased, reaching reliable differences by the fifth day. On the 7th day, this indicator began to increase again (Fig. 6, Table 6).

It should be noted that in 4 out of 10 people, the concentration of the proinflammatory cytokine was fundamentally different from the rest of the group. At the same time, when they were excluded from the sample, the trend of changes remained the same. This reflects significant individual characteristics and was the reason for using nonparametric statistical methods.

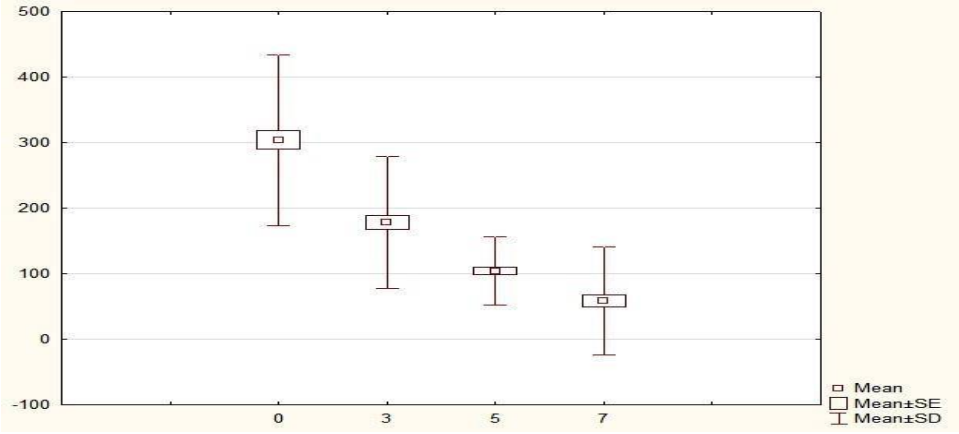

Figure 6. IL-1b concentration (pg/ml) in saliva on days 0, 3, 5, and 7 from the start of Laetrile treatment.

The values on day 5 differ significantly from days 0 and 3 with an error probability of 0.05 according to the Wilcoxon test for dependent samples. The change in the concentration of anti-inflammatory cytokines was generally inverse. Its relatively low concentration before the start of local treatment of oral mucositis was 31.68±5.91 pg/ml, gradually increasing by the 7th day. Three patients also differed significantly in this indicator, in whom IL-10 was significantly lower than in the others (in terms of IL-1b, these patients also had low values, which may be a criterion for exclusion

from the sample). When they were excluded from the sample, the trend did not change and represented a steady increase in the concentration of anti-inflammatory cytokines over time (Fig. 6, Table 6).

Table 6.Mean saliva concentrations in patients treated with Laetrile (M±SD)4.

Marker	Days from the start of treatment			
	0	3	5	7
IL-1b, пг/мл	303,99±130,18	178,57±100,71	104,02±51,86*	58,23±82,72
IL-10, пг/мл	31,68±5,91	111,06±68,95*	215,63±95,82*	311,85±122,31*

From this we can conclude that the existing therapeutic potential of Laetrile has a rapid local effect, reflected in the cytokine profile of saliva, but dynamically and unstable due to the more powerful systemic effect of ionizing radiation and chemotherapy. There is also a significant individual difference in sensitivity to both radiation and local therapy. The clinical and morphological positive data on the effects of Laetrile that we have previously identified make the results convincing in combination and indicate the autonomy of tissue reparative potential and the auxiliary effect of humoral factors in oral fluid.

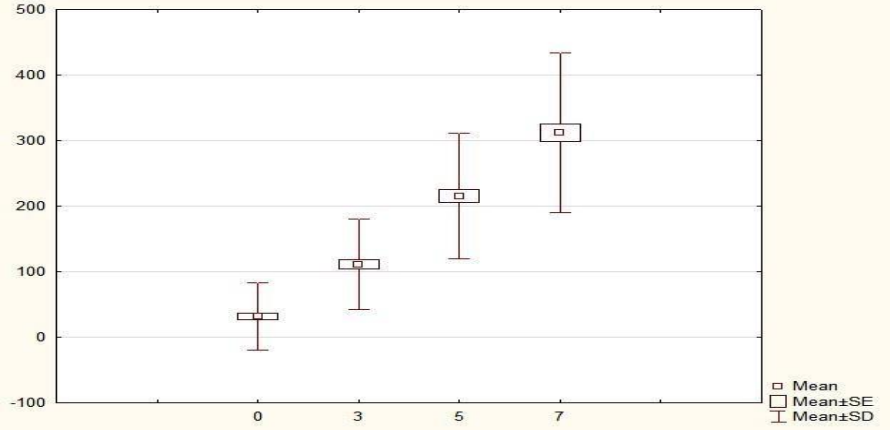

Figure 7.IL-10 concentration (pg/ml) in saliva on days 0, 3, 5, and 7 from the start of Laetrile treatment. The differences between all groups are significant, except for day 5 (no differences from days 3 and 7) with an error probability of 0.05 according to the Wilcoxon test for dependent samples.

The IL-1b/IL-10 ratio before treatment averaged 15-18 units. After treatment, this ratio rapidly declines during the first three days, then the decline slows down, while significantly differing from the control group on days 3, 5, and 7 (Fig. 8).

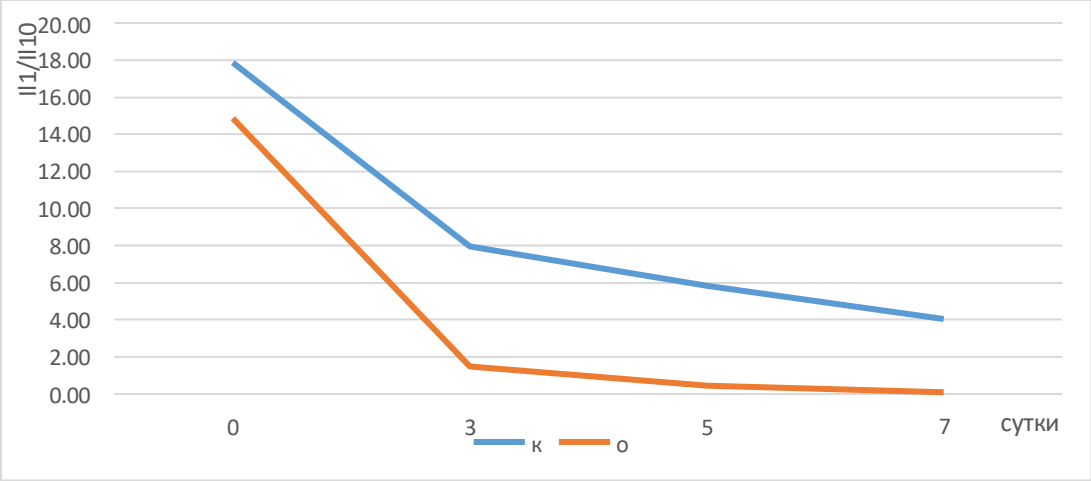

Figure 8. IL-1b/IL-10 M [Q1;Q4] ratio

Thus, Laetrile has a rapid local effect, reflected in the cytokine profile of saliva, which is quite dynamic due to the more powerful systemic effect of ionizing radiation and chemotherapy: the concentration of IL-1b by the 5th day decreases almost threefold, and IL-10 increases almost 7 times. A significant individual difference in the content of these cytokines was revealed, reflecting sensitivity to both radiation and local therapy. From the anamnesis it was revealed that 39 (43.8%) patients suffered from cardiovascular diseases, 32 (35.9%) patients had pathology of the nervous system, 13 (14.6%) had pathology of the thyroid gland, 12 (13.5%) were diagnosed with diabetes mellitus, 4 (4.5%) had pathology of the respiratory system, 3 (3.4%) patients indicated the presence of infectious diseases, two of them had viral hepatitis, and one examined person had tuberculosis and two people indicated occupational hazards.The level of oral hygiene of patients in both groups before and after treatment is presented in Table 7.

Table 7. Level of oral hygiene of patients in both groups

Reference values of the hygiene index	Hygiene Index Assessment	Oral hygiene assessment	Before treatment		Comparisons group		Main group	
					After treatment		After treatment	
			N=89	(%)	N=30	(%)	N=59	(%)
0–0,6	low	good	7	7,87	4	13,33	12	20,34
0,7–1,6	medium	satisfactory	21	23,60	8	26,67	30	50,85
1,7–2,5	high	unsatisfactory	31	34,83	9	30,00	11	18,64
2,6–3,0	very high	bad	30	33,71	9	30,00	6	10,17

Note: N – number of patients

The level of gum inflammation in patients in the comparison group during treatment was different and is presented in Table 7. Thus, the assessment of oral hygiene in patients in the comparison group is significantly worse than in the main group. In particular, the assessment of the hygiene index “very high” in the control group is 30.00%, which is significantly higher than in the main group (10.17%).

Table 8. Level of gum inflammation in patients in the comparison group during treatment

Control group (n 30)								PMA Value %	Degree of damage gingivitis
Before treatment		After treatment							
		Day 3		Day 5		Day 7			
Quantity	%	Quantity	%	Quantity	%	Quantity	%		
3	10	2	6,67	2	6,67	3	10,00	до 25	light
10	33,33	3	10,00	3	10,00	3	10,00	25-50	medium
17	56,67	3	10,00	3	10,00	8	26,67	> 51	heavy

The level of gum inflammation in patients of the main group during the treatment was also different and is presented in Table 9.

Table 9. Level of gum inflammation in the main group during the treatment

Main group (n 59)								PMA Value %	Degree of damage gingivitis
Before treatment		После лечения							
		Day 3		Day 5		Day 7			
Quantity	%	Quantity	%	Quantity	%	Quantity	%		
9	15,25	4	6,78	6	10,17	6	10,17	До 25	light
18	30,51	5	8,47	9	15,25	10	16,95	25-50	medium
32	54,24	4	6,78	8	13,56	7	11,86	более 51	heavy

Thus, severe gingivitis on the 7th day of treatment in the main group is 11.86%, moderate gingivitis was detected in 16.95%. The level of gum inflammation in patients in the main group after treatment is significantly lower than in the control group. This indicates the same tendency to improve the condition of the gums and reduce inflammatory processes in them. The use of Laetrile made it possible to achieve a therapeutic and prophylactic effect in 55 (93.2%) of 89 patients treated with Laetrile while in the comparison group (traditional treatment) in 19 (63.3%) of 30 patients. The effectiveness of the therapy can be conveniently demonstrated figure 9a,b.Patient M., 53 years old, Diagnosis: tongue cancer T3N0M0 Mucositis grade III.

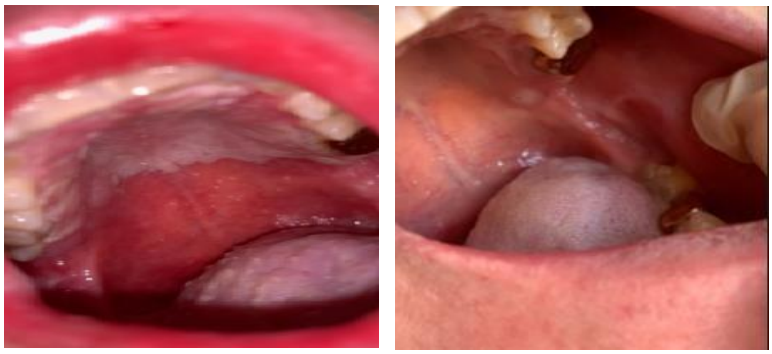

Figure 9. a) – Before treatment **Figure 9. b)** After treatment

Clinical case: Patient I., 58 years old (main group) was admitted to the State Budgetary Healthcare Institution of the Republic of Crimea "V. M. Efetov Crimean Republican Oncology Clinical Dispensary" with a diagnosis of oral mucosa cancer T3N0M0 after the first course of chemotherapy. A few minutes before radiation therapy, a protective device was put on the patient on both parotid areas. After that, distant gamma therapy was performed. SOD 48 -50 Gy. Before irradiation, we used protective mouth guards to prevent the development of radiation sickness of the oral cavity. During treatment (3-4 days), the patient complained of dry mouth, pain when swallowing solid food. Mild mucositis was detected. Tooth mobility of the II degree. Upon examination of the patient, it was revealed that the mucous membrane was slightly hyperemic - edematous. The index assessment of the state of the oral organs is: KPU = 22, GI - 2.5; RMA – 53%. On the 5th day, the patient complained of dry mouth, mild bleeding gums, exposed necks of teeth, pain when swallowing solid food. Regional lymph nodes are normal, oral mucosa is hyperemic, dry, edges of interdental papillae and alveolar processes of the upper and lower jaws are stagnant and edematous, abundant deposits of soft plaque of supra- and subgingival tartar. Periodontal pockets up to 4 mm deep, bad breath. Tooth mobility of the 2nd degree. Single erosive erythematous foci were observed in the oral cavity. Moderate mucositis was detected. On the 7th day, the patient complained of dry mouth, bleeding gums, exposed necks of teeth, pain when swallowing any kind of food. Regional lymph nodes are painful and enlarged, oral mucosa is clearly hyperemic, multiple erosive and ulcerative lesions are observed in the oral cavity, bleeding is noted, the edges of the interdental papillae and alveolar processes of the upper and lower jaws are stagnant and edematous, there are abundant deposits of soft plaque, supra- and subgingival tartar with purulent-hemorrhagic discharge. Periodontal pockets are 6 mm deep, there is an unpleasant odor from the mouth. Tooth mobility of II - III degree. III degree of mucositis was revealed). The status during examination is illustrated in Fig. 10a,b.

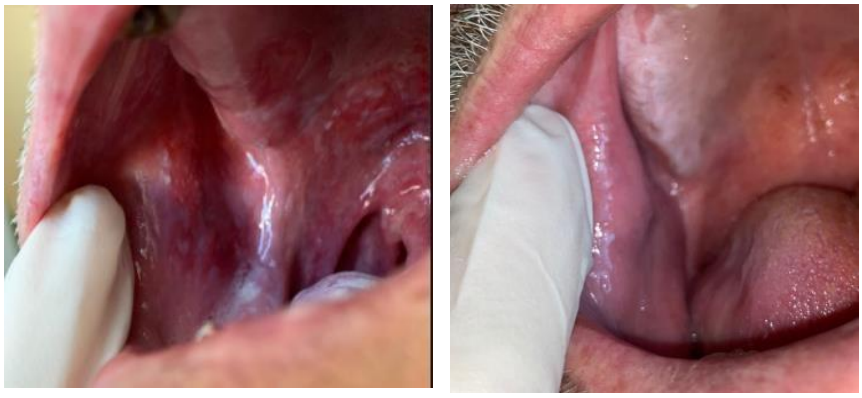

Figure 10. Patient I, 58 years old, Diagnosis: oral cavity cancer T3N0M0. a) – Before treatment. b) After treatment.

DISCUSSION

Chemotherapy and radiotherapy are the predominant treatment options for patients with oncological and oncohematological diseases. The use of these two antitumor agents increases the frequency and severity of side effects, which can lead to severe mucositis.

A number of chemotherapeutic preparations and their combinations are used for chemotherapy of malignant neoplasms of the organs and tissues of the mouth. These include bleomycin, cisplatin, carboplatin, fluorouracil, paclitaxel, docetaxel. The most important antitumor drug in the treatment of this localization is cisplatin. Despite the understanding of the causes and mechanisms of oral mucositis, it remains a serious problem for patients receiving treatment for localized head and neck cancer. The severity of mucositis varies greatly and depends on the treatment methods used (total radiation dose, volume and area of irradiation, fractionation regimen, use of chemotherapy) and on the patient-related risk factors (gender, age, lifestyle, presence of carious teeth, concomitant diseases, epigenetic and genetic susceptibility)[34].

Today, several Classification are available to assess the severity of oral mucositis. Staging according to the Radiation Therapy Oncology Group (RTOG) is performed on a scale from I to IV. The first degree includes mucositis that causes mild pain and does not require the use of analgesics[35].

Grade II is typical for the development of focal mucositis or mucositis requiring the use of analgesics.

Grade III mucositis occurs in the form of confluent mucositis or is accompanied by pain syndrome requiring narcotic analgesics.

Grade IV is characterized by the formation of ulcers, areas of necrosis or bleeding.

Oral mucositis associated with treatment in such patients, reduces the quality of life of patients and increases the risk of life-threatening complications To decide on the treatment method for oral mucositis, it is necessary to assess the severity of the disease in a particular patient, which is determined by the methods of prevention and treatment aimed at increasing the patient's tolerance to the treatment and reducing the risk of complications associated with the treatment.

Treatment of oral mucositis is pathogenetic and symptomatic.

There are currently no generally accepted protocols for the prevention and treatment of oral mucositis.

The Mucositis Study Group of the Multinational Association for the Treatment of Cancer (MASCC) and the International Society for the Study of Oral Oncology (ISOO) developed clinical practice guidelines for the treatment of oral mucositis based on a comprehensive systematic review of the literature[36,37] .

From the moment of manifestation of radiation epitheliitis and until the complete subsidence of reactions, the use of wound-healing local agents, irrigation of the oral cavity with an isotonic solution, applications of oils (olive, peach, sea buckthorn or rose hips) to the oral cavity is indicated. In the presence of pain syndrome, local and systemic painkillers are used [38].

Pain relief should be prescribed in accordance with the scale of the World Health Organization. Adequate nutrition and maintenance of water balance are vital. A special role is played by the balance of food intake, which reflects the maintenance of a stable weight. Often, it is necessary to prescribe oral nutritional mixturesAttention is paid to the role of oral hygiene, the use of physical methods (hypothermia, laser therapy), the prevention of infectious complications, and the use of local and general epithelialization-stimulating agents. All of these methods have their positive and negative sides, advantages and disadvantages. Often, the methods are complex, multi-component, require the use of expensive drugs and expensive equipment manufactured abroad.

The goal of treatment of oral mucositis during radiotherapy is to prevent the development of severe oral mucositis and associated secondary infections, as well as to control pain and maintain the ability to eat independently. treatment is carried out with an emphasis on palliative care and symptom control [8]. However, symptomatic therapy does not always achieve adequate pain control, which only emphasizes the importance of developing new treatment strategies[39,40].

Currently, the are considering several groups of means for the prevention of mucositis and treatment of oral mucositis: anti-inflammatory drugs, antimicrobial agents, biological response modifiers, antioxidants, non-pharmacological effects. It is important to note that reducing morbidity may positively impact treatment tolerability, compliance, and quality of life for patients.

Prevention of mucositis mainly comes down to oral hygiene before chemotherapy, visiting the dentist (in the presence of carious teeth and manifestations of periodontitis).

Randomized trials have shown the effectiveness of topical and systemic antimicrobial drugs for the prevention and treatment of oral inflammation[41].

However, antimicrobial drugs also have a number of cytotoxic side effects, which are undesirable in oncological patients who are already receiving high doses of drugs that have an immunosuppressive effect. Therefore, the search for such means and methods that do not have a toxic effect on the oral mucosa and the patient's body as a whole is certainly of scientific interest.

To increase the effectiveness of chemotherapy and chemoradiotherapy for oncological diseases, it is necessary to search for and develop highly effective means for the prevention and/or treatment of various forms of inflammation of the oral mucosa that are affordable, have low toxicity, do not require the use of special equipment, and are suitable for patients both in hospital settings and at home.

The search for methods and means to minimize the impact of an unsanitized oral cavity and effectively prevent mucositis continues to be relevant.

In this work, a herbal preparation was used to increase the effectiveness of methods for preventing and treating inflammation of the oral mucosa in patients. To solve the set tasks, groups of patients receiving radiation or chemoradiation therapy for squamous cell carcinoma of the oropharyngeal region were formed.

A herbal preparation Laetrile was used, the results obtained in the work confirm the effectiveness of the proposed schemes for the prevention and treatment of mucositis in cancer patients against the background of radiation and/or chemotherapy treatment both in clinical (reducing the severity of mucositis and improving the quality of life of patients),

CONCLUSION

The use of Laetrile has reduced the incidence of bleeding gums, erosions and ulcers of the oral mucosa. Its use is recommended for mucositis causing complications chemo- and radiation therapy.

DECLARATIONS

Ethical approval and consent to participate
The work was carried out in compliance with all ethical standards for conducting an experiment and there is a positive decision of the Ethics Committee of the Order of the Red Banner of Labor Medical Institute named after S. I. Georgievsky.

Competing interest

The authors declare that there are no competing interest.

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Authors' contribution

Inessa Romanenko - study design, data collection and analysis, writing the text;

Kristina Arakelyan development of the research methodology and interpretation of the obtained data, preparation of the manuscript

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