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HEMOMICROCIRCULATION OF THE ORAL MUCOSA AS AN EFFICIENCY INDICATOR OF LOCAL TREATMENT AND PREVENTING COMPLICATIONS FROM RADIATION AND CHEMOTHERAPY FOR HEAD AND NECK MALIGNANCIES

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ABSTRACT — Background: Mucositis is a common and severe complication of anti-tumour therapy. The use of plant-derived drugs in patients with malignant neoplasms of the oral mucosa and maxillofacial area according to a certain group of dental risks shows good results and can be considered as one of the promising methods for the prevention and treatment of mucositis. One of the methods confirming the effectiveness of the local treatment is the determination of hemomicrocirculation in the tissues of the oral mucosa.
Objectives: To determine the state of hemomicrocirculation in the tissues of oral mucosa in patients with oropharyngeal squamous cell carcinoma at different stages of anti-tumour therapy, as well as during the application of different methods for local treatment of oral mucositis.
Materials and Methods: From January 2017 to May 2018, in the Department of Radiotherapy of the National Medical Research Radiological Centre (NMRRC) of the Russian Federation, the microcirculatory parameter (MP) of hemomicrocirculation was determined in 69 patients diagnosed with oropharyngeal squamous cell carcinoma.
Results: In group I, hemomicrocirculation was higher at all measurement points than in group II. Clinical manifestations of oral mucositis in group I develop later than in group II and correspond to the maximum value of hemomicrocirculation in each group.
Conclusions: The results confirm that the use of long-acting plant-derived drugs is more effective than traditional oral irrigation with chamomile decoction and oleotherapy for the prevention and treatment of oral mucositis: Decrease in microcirculation indicators of group I (using the drugs) is 7.4% less than one of group II (not using the drugs); $p < 0.04$.

KEYWORDS — mucositis, hemomicrocirculation, long-acting plant-derived drugs.

BACKGROUND

From 2017 to 2018, on the basis of the National Medical Research Radiological Centre (Ministry of Health of Russia), we determined the microcirculatory parameter (MP) of oral mucosa in four randomly selected points in 69 patients with oropharyngeal squamous cell carcinoma before radiotherapy at its various stages and after radiotherapy in the background of the local treatment of mucositis with the use of long-acting plant-derived drugs. The results showed their effectiveness for the prevention and treatment of oral mucositis, compared with common methods of irrigation cleansing to oral cavity with chamomile decoction and oleotherapy. The results also revealed the dependence of hemomicrocirculation in oral mucosa in patients with oropharyngeal squamous cell carcinoma on the severity of clinical manifestations of mucositis.

Cancer incidence continues to grow steadily, according to both Russian statistics and global indicators[4, 5]. An increase in the incidence of malignant neoplasms of the oral mucosa in Russia over the past 10 years has amounted to more than 30% [5].

Squamous cell carcinoma of varying degrees of differentiation is the predominant morphological variant among tumours of the oral mucosa. Certain sensitivity of these tumours to radiation and drug exposure, as well as primary neglect of the process and difficulty in performing surgical interventions made it necessary to use chemotherapy and radiotherapy that are sometimes the only forms of treatment for the above pathology [8].

Optimisation of chemotherapy regimens and use of conformal radiotherapy in the treatment of oropharyngeal squamous cell carcinoma decreased the frequency of its relapses and increased the average life expectancy of patients [14]. However, the frequency of occurrence of related complications such as, infectious, hemorrhagic, destructive, erosive-ulcerative and necrotic changes of the mucous membranes (mucositis), including in the oral cavity, remains at a high enough level. According to the European Society for Medical Oncology, the incidence of grade III–IV mucositis on the WHO scale reaches 85% among patients

receiving radiotherapy for the head and neck, but all patients who have received treatment have one or the other degree of mucositis [15].

Radiation mucositis, one of the most severe and often documented complications of anti-tumour therapy, can be the beginning of the development of severe enteropathy and often, the cause of death [16]. The development of mucositis leads to the interruption of the routes of ongoing anti-cancer treatment, thereby reducing its effectiveness, adversely affecting the prognosis of the disease [17]. Additionally, mucositis significantly increases the cost of treatment, the duration of hospitalisation and cost of medicines.

Much attention is paid to the study of the mechanisms of development of radiation and chemotherapeutic injuries of the oral mucosa in the treatment of cancer and oncohematological patients [6, 7, 9, 10, 11].

Currently, the main pathogenetic theory of the development of oral mucositis is the S. Sonis concept [9], divided into five stages of mucositis development: 1) initiation; 2) primary damage; 3) generation and amplification of signals; 4) ulceration; 5) healing.

According to literary sources [2], the study of the regulation of the microcirculation system in the tissues of oral mucosa allows the evaluation of functional changes' role, development of therapeutic interventions and determination of their effectiveness.

In a number of publications [1, 3, 4, 12], the vascular factor is brought to the forefront in the pathogenesis of radiation injuries of the oral mucosa; a change in vascular permeability leads to hypoxia and impaired trophism of irradiated tissues with subsequent structural degradation of the oral mucosa.

In connection with the above, the determination of blood microcirculation parameters in the tissues of oral mucosa in patients receiving radiation and/or chemoradiation therapy is of great scientific and practical interest.

OBJECTIVE

To determine the state of hemomicrocirculation in the tissues of oral mucosa in patients with oropharyngeal squamous cell carcinoma at different stages of anti-tumour therapy, as well as during the application of different methods for local treatment of oral mucositis.

MATERIALS AND METHODS

The inclusion criteria for this study includes patients who were diagnosed with oropharyngeal squamous cell carcinoma and aged 18–75. From January 2017 to May 2018, in the Department of Radiotherapy of the FSBI NMRRC of the Russian Federation, the MP of hemomicrocirculation was determined in 69 patients diagnosed with oropharyngeal squamous cell carcinoma.

The average age of patients was 54 years; 62% were men (42) and 38% women (27).

All patients had morphologically confirmed diagnosis of oropharyngeal squamous cell carcinoma.

Localisation was dominated by tongue injuries (32%), bottom of the mouth (20%) and oropharynx (24%). Among other sites of injury were lips, cheeks, and the alveolar bone on the lower jaw.

In majority of patients, the stage of disease T2N0M0 (39%), T3N0M0 (16%), or T3 N1M0 (20%) was established.

Burdened somatic history was observed in almost all patients over 50 years. In 32 patients (64%), associated chronic diseases were noted (asthma, chronic obstructive pulmonary disease and diabetes, pathology of the gastrointestinal tract). Most patients (78%) had more than one pathology.

Anti-tumour therapy in patients with oropharyngeal squamous cell carcinoma was carried out according to the standards of treatment for malignant neoplasms. At the first stage, patients underwent radiation treatment due to their refusal from surgical treatment or the presence of contraindications for surgical treatment. Remote radiotherapy was used in a separate version. Radiotherapy was delivered using a linear accelerator Clinac C2100 (Varían) in the bremsstrahlung mode with a photon energy of 6 MV.

Patients were divided into two groups, based on their voluntary consent to follow the recommendations of the dentist and to use prescribed treatment regimens for the prevention and treatment of oral mucositis.

Group I included 45 patients, who used prescribed by a dentist long-acting plant derived drugs *Tonsinal* (1 sachet contains water-soluble extracts of Hypericum herb, calendula flowers, yarrow grass, licorice root, rose hips, sea salt, decamethoxin, citric acid, lactose) and plate *CM-1* (1 sachet contains hypericum herb extracts, yarrow, sage, vitamin C, gelatin) for the prevention and treatment of oral mucositis in the background of anti-tumour therapy. These drugs are known as herbal medicines in Russia. The method of treatment included the use of drugs not only for their intended purpose and recommendations, but also daily oral care in the dental clinic: irrigation of the oral cavity with *Tonsinal* solution (1 powder per 300 ml of water) with the addition of 1 tsp. olive oil 4–6 times per day, as well as the application of plates *CM-1* on the mucosa of the cheeks on the right and left sides, twice every day for three to four hours. The total number of hours of direct exposure to oral mucosa was seven to eight hours.

Group II comprised 24 patients, who used oral irrigation with chamomile decoction (essential oils, resins, carotenoids, organic acids, flavonoids, phytosterol, choline, as well as vitamins B1, B2 and carotene) and vegetable oil (castor oil) for the prevention and treatment of oral mucositis in the background of the anti-tumour therapy.

The determination of the MP of hemomicrocirculation was carried out before radiotherapy, as well as at its stages with a total tumor dose of 8–18 Gy, 20–28 Gy, 30–38 Gy, 40 or more Gy at four randomly selected points: A — alveolar mucosa (near the gums) in the area of teeth 31 and 41; B — lower lip mucosa in the projection of the attachment site of the bridle; C — cheek mucosa in the projection of teeth 16, 17; D — mucosa of the bottom of the mouth in the projection of the attachment site of the tongue frenulum. The study was conducted with the help of the LAKK-M apparatus (second version), using a laser Doppler flowmetry (LDF) on the basis of FSBI NMRRC of the Russian Federation.

MP determines the dynamic characteristics of the microcirculation of blood — the change in blood flow (tissue perfusion) per unit time in the studied tissue volume of about 1 mm^3 in relative perfusion units *pf*. The LDF signal has a constant and a time-variable component, associated with the tone of the microvessels. The stationary component of the tone is due to the constant component of MP, while the variable component comprises active factors controlling the regulation of the vessel lumen, mediated by endothelial, neurogenic and myogenic mechanisms.

Given the small number of observations, statistical processing was carried out using the sign test (a non-parametric method).

In our study, ethical approval was obtained from the Ethics Committee of Institute of Medicine, Peoples' Friendship University of Russia (No. 0212), Moscow, Russia.

RESULTS AND DISCUSSION

The results of determining the MP of hemomicrocirculation are presented in Table 1 and Fig. 1, 2.

As shown in table 1, the rate of MP in patients in groups I and II before radiotherapy is higher than after radiotherapy, at all points of measurement. This is explained by the effect of radiotherapy on vascular mechanisms and atrophy of vascular endothelium cells under the effect of radiotherapy, corresponding to literary sources. At the same time, in group I at point A, hemomicrocirculation indicators decrease by 49.6% compared with the baseline. In contrast to group II, indicators at point A decrease by 57.0%, $p < 0.04$.

At points B, hemomicrocirculation indicators decrease by 64.9% compared with the baseline. In contrast to group II, indicators at point B decrease by 90.2%, $p < 0.03$.

At points C, hemomicrocirculation indicators decrease by 5.8% compared with the baseline. In contrast to group II, indicators at point C decrease by 34.4%, $p < 0.04$.

At points D, hemomicrocirculation indicators decrease by 44.05% compared with the baseline. In contrast to group II, indicators at point D decrease by 54.1%, $p = 0.0678$.

At each measurement point, the difference is from 10 to 30%. These indicators confirm the effectiveness of the local treatment with the use of long-acting drugs in group I.

Figure 1 shows that MP in patients in groups I and II varies in different ways throughout the radiotherapy phase.

In group I, microcirculation indicators increase to a maximum point achieved with a dose of 20–28 Gy, on average corresponding to the first clinical manifestations of oral mucositis in patients of this group (hyperemia, mucosal edema), with subsequent decrease to 49.6% from the initial indicators. In group II, microcirculation indicators increase to a maximum point with a dose of 8–18 Gy, on average corresponding to the first clinical manifestations of oral mucositis in patients of this sub-group, with subsequent decrease to 57% from the initial indicators.

CONCLUSION

The results confirm that the use of long-acting plant-derived drugs is more effective than traditional oral irrigation with chamomile decoction and oleotherapy for the prevention and treatment of oral mucositis: Decrease in microcirculation indicators in group I (using the drugs) is 7.4% less than one group II (not using the drugs); $p < 0.04$.

The dependence of the onset of clinical manifestations of mucositis on the maximum MP of hemomicrocirculation indicators reflects the possibility of considering hemomicrocirculation as a predictive factor for the development of mucositis.

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Table 1. *The results of measuring MP in patients with squamous cell carcinoma in the background of radiation and/or chemotherapeutic therapy (M is the average MP value in the group. δ is the standard deviation)*

MP	Localisation of measurements			
	Alveolar mucosa (near the gums) in the area of teeth 31. 41 (Point A) M. δ	Lower lip mucosa in the projection of the attachment site of the bridle (Point B) M. δ	Cheek mucosa in the projection of teeth 16. 17 (Point C) M. δ	Mucosa of the bottom of the mouth in the projection of the attachment site of the tongue frenulum (Point D) M. δ
Group I				
Before therapy	38.8 ± 3.68	15.4 ± 3.3	34 ± 1.9	37.5 ± 5.6
8–18 Gy	38.0 ± 1.9	28.3 ± 1.1	37.5 ± 5.65	35.6 ± 1.1
20–28 Gy	40.25 ± 5.15	41.4 ± 13.4	36.15 ± 4.65	48.2 ± 8.7
30–38 Gy	39.3 ± 1.1	45.4 ± 1.1	45.4 ± 1.1	48.7 ± 1.1
≥ 40 Gy	19.6 ± 0.01	5.4 ± 1.1	32.0 ± 0.01	22.3 ± 0.01
Group II				
Before therapy	35.8 ± 0.01	24.5 ± 7.0	34.0 ± 1.9	33.6 ± 0.01
8–18 Gy	43.6 ± 9.3	42.8 ± 13.7	45.4 ± 1.1	69.4 ± 26.7
20–28 Gy	32.7±0.01	36.8 ± 1.2	32.0 ± 0.01	47.85 ± 15.1
30–38 Gy	28.8±3.68	18.3 ± 0.01	32.0 ± 0.01	47.85 ± 15.1
≥ 40 Gy	15.4 ± 3.3	2.4 ± 1.1	22.3 ± 0.01	15.4 ± 3.3

Fig. 1.

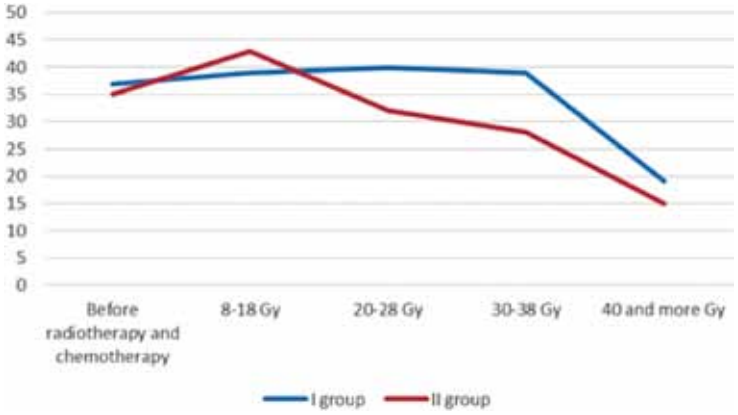

Fig. 2. *Dynamic change in MP at point A (periodontal region in the projection of teeth 31, 41) in patients with oropharyngeal squamous cell carcinoma using long-acting drugs (group I) and patients using chamomile decoction and oleotherapy for oral irrigation (group II). The ordinate axis shows MP*

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