

Research Article

Efficiency of local application of a new hygienic agent during treatment of radioreactions of oral mucosa in patients with tumors of head and neck region after the radiation therapy

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The article deals with topical application of a new medication “Apior” gel in the complex therapy of radiation complications in the oral cavity of patients with tumors of head and neck region undergoing radiation treatment. It was proved that the new apigel subsides pronouncement of symptoms of xerostomia and oral radioreactions, arrests them, improves hygienic state of oral cavity, salivation, positively affects nonspecific resistance of oral fluid, rendering a radioprotective action. A positive effect of “Apior” gel is reached due to renewal of balance of pro- and antioxidant activity, reduction of level of pro-inflammatory (i.e., IL-1 and IL-6) and rise of anti-inflammatory (i.e., IL-4) cytokines level, restoration of secretory immunoglobulin A, normalizes oral microbiocenosis.

Keywords: radiation therapy, “Apior” gel, pro-inflammatory (IL-1, IL-6), anti-inflammatory (IL-4) cytokines.

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Introduction

Radiation therapy, applied both independently (palliative treatment) and in the complex treatment with surgery or chemotherapy, according to the statistical data, it is the one of most effective methods for treating malignant tumors, which allows to extent life-span of oncologic patients and improve their clinical recovery. In spite of improvement of high-power sources of radiation, involving the regional metastasis, which improves recovery, there are detected the increased radioreactions rates and complications of surrounding healthy tissues and organs [1, 2].

The violation of physiological defense of organism under conditions of irradiation in head and neck region results in destruction and damage of lipids of membranes, enzymes, glycoproteids etc. which lead to local radioreactions in the oral cavity, such as hyperemia and edema of the mucous membrane, accompanied with sense of burning, pain, taste sensitivity. Radiation complications are characterized with long-term progressing clinical course combined with the infectious agents, which result in

development of inflammatory diseases, and violations of trophism and metabolism in the irradiated tissues as well [3, 4]. These particular radioreactions and complications in the oral cavity are the causes of a forced gap and an increase in duration of specific treatment, development of functional violations in the masticatory-vocal apparatus, problems in feeding, decline of life quality. Ineffective medical measures, duration of treatment and rehabilitations, performance decrement determine actuality of problem, its medical, economic and social importance. As a result, it appears a necessity to develop curative-preventing measurements and extension of their application to improve the efficiency of radiation therapy for oral mucosa (OM) and complications in the oral cavity.

The Purpose of this research is estimating efficacy of topical use of the developed gel “Apior” in the complex treatment of radiation complications in the oral cavity in patients with the tumors in head and neck region after the conducted radiation therapy.

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Materials and methods

A complex dental examination of 42 patients aged 42–68 years was conducted. All the patients had radiation therapy during combination therapy of tumors in region of head and neck. The time passed after the end of irradiation is more than 1 month. Patients were divided into 2 groups: control and basic. Routine medical measurements were performed in the control group (20 persons): sanitation, irradiation and oral hygiene, oral rinsing with antiseptic solutions, herb tea (chamomile, sage), treatment of injured OM regions with olive oil. For pain relief during eating there was recommended lidocain 5 % gel, with dry mouth there was used a substitute of saliva (Oral balance).

The patients in basic group (22 men) besides the routine therapy were carried out topical applications with the developed gel “Apor” on injured sites of OM. “Apor” is based on biologically active substances [5], having antioxidant, anti-inflammatory, antimicrobial effects and accelerating processes of tissue regeneration. The patients processed OM by themselves with gel 3 times a day during 7–14 days.

The patients have been followed up for 1–2 years, the examinations were conducted before treatment, in 2 weeks, in 1 month, in 3, 6, 12, 15 months after treatment.

The clinical examination included questionnaire and objective exams. The following changes were revealed during examination of oral cavity, such as discoloration, presence of different pathological elements: bubbles, ulcers, crusts, spots etc. The state of excretory ducts of salivary glands, presence and quantity of the secreted discharge were determined, with signs of hypertrophy and instrumental examination of permeability. Salivation was evaluated by the volume of unstimulated and stimulated saliva.

According to pronouncement, there are three degrees of radiation-induced xerostomia: with complaints about dry mouth, but without a considerable decline of salivation (I degree), with the decline of salivation (II degree) and with pronounced manifestation of xerostomia syndrome (III degree).

A hygienic state of the oral cavity is determined by the Fyodorov–Volodkina index. With Schiller–Pisarev solution there oiled vestibular surfaces of teeth and estimated by five-point grading scale [6]. The presence and intensity of inflammation in gum were estimated by the PMA

(papillary marginal alveolar) index (Parma C. 1960), bleeding by the PBI (papilla bleeding index) Muhlemann and Saxer; pronouncement of pain syndrome by the visual-analog scale by ten-point grade scale [7]. The oral fluid was collected from an empty stomach [8]. Concentration malondialdehyde (MDA) was determined by the thiobarbituric method [9], activity of antioxidant defense was evaluated by catalase (K) activity [10].

Cytokines level IL-1, IL-6, IL-4, in the blood serum of patients was determined by the solid-phase antibody assay using the “Bender Medsystems” (Austria) and “Endogen” (USA) sets on the “Evolis TwinPlus” (BIORAD, USA) analyzer, by included user’s manual. Concentration of cytokines is calculated by calibration curves.

SIgA in the oral fluid was determined by the immunoenzyme method with the use of set of Joint-Stock SIgA-IFA-BEST-Company “Vector-Best” (Novosibirsk, Russia). In case of determination there used a solid-phase antibody assay, based on “sandwich” principle. The results were taken into account photometrically. SIgA level in tests was determined based on the calibration curves [12].

The microbiological examinations were conducted before treatment and one month after the treatment. Microbial flora was conducted in the oral fluid of patients. Sampling was performed with a sterile stick and transferred to a sterile test tube, poured with sugar broth and sent to the bacteriological laboratory, where qualitative and quantitative composition of selected microflora was determined. The inoculated material on solid culture media (bloody agar, egg-yolk-salt agar, the Ploskirev’s medium etc.) are for revealing dominant strains of bacteria. After a 24-hour incubation in thermostat at 37 °C, the morphology of obtained cultures (smears were stained by Gram) was conducted by bacterioscopy, and under the immersion microscope there were identified selected microorganisms [13]. For determination of anaerobic bacteria the Kitt–Tarozzi medium under conditions of anaerobic culture apparatus with the oxygen-free gas mixture were used. For estimation of quantitative growth of microorganisms there were calculated colony-forming units (CFU) by 1 ml of oral fluid and expressed in the common logarithm [14]. We calculated arithmetic mean value of the common logarithm for every CFU and the size of representative error.

The statistical analysis was conducted through the Excel 2003 and Statistica 6.0 program for Windows.

Results and discussion

After conducting radiation therapy (30–60 Gy) all the patients had the following symptoms: xerostomia, pain during eating, OM and lips reddening. OM changes were characterized by pronounced dry mouth, hyperemia, edema, loss of brightness, appearance of folds on the mucous membrane of cheeks, lips, rarer — on the soft palate. Hyperemia on the lateral surfaces of tongue was marked. Hyperemia, edema, rarer loss of brightness and folding on the hard palate were observed. Erosion covered with fibrin were localized mainly on the mucous membrane and red border of the upper lip.

The first examination of the patients revealed xerostomia of different degrees (I–III degree). In case of dysfunction of salivary glands, when salivation was fully violated (III degree), the pain in the salivary glands, acute dry mouth, pain at eating, violation of sleep, speech. There were

phenomena of stomatitis, dry mouth, hyperemia, with cracks, erosions. Lips are dry, desquamated, crusty. There is often multiple caries.

In the process of examination, it revealed that the degree of xerostomia pronouncement depends directly on the radiation dose. At the cumulative dose 50–60 Gy. The symptoms typical for the III degree of xerostomia were observed for 1.5–2 years.

Under our observation there were patients with xerostomia of I and II degrees, the dynamics of symptoms depended on the time, which had passed since the moment of radiation therapy, showing a reversible process, which was the evidence of absence of structural defeats of salivary glands.

Renewal of salivation in oncologic patients after the radiation therapy is a rather long process, and in the basic group of patients, it was more saliva secretion and faster than control group (Table 1).

Table 1. Dynamics of xerostomia pronouncement in dental treatment of oncologic patients after the radiation therapy in region of head and neck, abs. (%)

Degree of xerostomia	Control group (n=20)				Basic group (n=22)			
	Before treatment	1 months	6 months	1 year	Before treatment	1 months	6 months	1 year
I	10 (50)	6 (30)	4 (20)	2 (10)	14 (63.6)	8 (36.4)	3 (13.6)	2 (9.1)
II	6 (30)	4 (20)	4 (20)	3 (15)	5 (22.7)	3 (13.6)	2 (9.1)	1 (4.55)
III	4 (20)	4 (20)	3 (15)	2 (10)	3 (13.6)	2 (9.1)	2 (9.1)	1 (4.55)
Norm	-	6 (30)	9 (45)	13 (65)	-	9 (40.9)	15 (68.2)	18 (81.8)

After the irradiation, all patients had impaired secretory function of salivary glands and in the patients of the control group before stimulation on average (0.44±0.02) ml/min, after stimulation (1.14±0.03) ml/min, in the patients of the basic group, before stimulation — (0.45±0.02) ml/min, after stimulating — (1.08±0.04) ml/min. Impaired salivation, caused by influence of radiation therapy, in the process of supervision recovers or reaches to the normal figures. Reliable distinctions in renewal of indices of secretory function of salivary glands in patients of both groups were not revealed.

As a result of dental examination there were established symptoms of the radioreactions of OM: hyperemia, edema, gums bleeding, erosion and ulcerative-necrotic processes,

Hygienic state of the oral cavity before the beginning of treatment in 61 % patients was estimated as unsatisfactory. Applications with gel in combination with the professional hygiene considerably improved the level of hygiene of oral cavity. So, the index of hygiene of the oral cavity from (2.48±0.30) points decreased 1.5 times after the conducted

focal and confluent epithelitis. 50–60 % patients after irradiation (20–40 Gy) suffered from radiation stomatitis, hyperemia of mucous membrane. There were observed development of edema and erosions of mucous membrane, bleeding of gums, rarer — phenomena of focal and confluent epithelitis after the irradiation by the total dose 40–60 Gy.

In the process of treatment in the basic group, the displays of radiation complications substantially subsided: bleeding of gums, OM erosions and ulcers were revealed 2 times rarer in a month after the treatment, than in the control group. Ulcers, phenomena of necrosis and confluent epithelitis were not revealed in any patient of this group at this time (Table 2).

treatment, at the traditional therapy the index of hygiene decreased on average down on 0.23 points (Table 3).

The application of the new gel resulted in reduction of bleeding of gums on average 3.3 folds from 2.86±0.11 to 0.87±0.10 (before and after treatment), in the control group

a decline is less expressed — on average from 2.92 ± 0.09 to 1.32 ± 0.14 , so 2.2 times.

Reduction of signs of inflammation was confirmed by the positive dynamics of the PMA index in both groups of patients, the more intensive anti-inflammatory reaction was

in the basic group. By the end of treatment the PMA index in patients during an ordinary therapy decreased from 45.30 ± 2.40 to 14.8 ± 1.28 , meanwhile in the patients of basic group — from 43.25 ± 1.68 to 6.40 ± 1.31 .

Table 2. Frequency of local displays of radioreactions in patients with the tumors in head and neck region after the radiation therapy in the process of treatment

Objective symptoms	Control group (n=20)				Basic group (n=22)			
	Before treatment	2 weeks	1 month	3 months	Before treatment	2 weeks	1 month	3 months
Hyperemia	9	5	2	2	9	4	0	0
Edema	6	4	3	3	8	3	1	1
Bleeding of gums	9	6	4	2	7	3	2	1
Foci epithelitis	5	4	3	2	5	3	1	0
Confluent epithelitis	2	1	0	0	3	1	0	0
Ulcers	4	3	2	0	4	2	0	0
Necrosis	2	2	1	1	1	1	0	0

As radiation complications in the oral cavity are accompanied by pain of different extent, great importance was paid to the analysis of anaesthetic effect of “Apior” gel. In the patients of basic group after conducting applications with the new gel the pain syndrome decreased on average from 7.00 ± 0.28 to 2.14 ± 0.10 , in patients of the control group the pain syndrome reduced from 7.80 ± 0.20 to 3.60 ± 0.18 .

Local application of “Apior” gel in the patients of the basic group temporally removed dry mouth, prevented from discomfort, OM state got better, positive changes of qualitative signs of oral fluid (viscosity, foaminess decreased) were marked, which considerably improved life quality of patients. The patients could eat without the pain syndrome and rarer rinse the oral cavity or use artificial saliva.

Table 3. Dynamics of clinical signs of the oral cavity in patients against a background of the conducted therapy

Indices	Groups of patients			
	Control (n=20)		Basic (n=22)	
	Before treatment	1 month of treatment	Before treatment	1 month of treatment
Index of hygiene of oral cavity, points	2.41 ± 0.32	2.18 ± 0.26	2.48 ± 0.30	1.74 ± 0.25
Ic		>0.05		>0.05
PMA	45.30 ± 2.40	14.8 ± 1.28	43.25 ± 1.68	6.40 ± 1.31
Ic		<0.05		<0.05
Index of bleeding	2.92 ± 0.09	1.32 ± 0.14	2.86 ± 0.11	0.87 ± 0.10
Ic		<0.05		<0.05
Estimation of pronouncement of pain syndrome (by ten-point scale)	7.80 ± 0.20	3.60 ± 0.18	7.00 ± 0.28	2.14 ± 0.10
Ic		<0.05		<0.05

Note: I — index of reliability of differences with group “before treatment”; Ic — index of reliability of differences with the “control” group.

Table 4. Influence of complex treatment on the biochemical indices of oral fluid in patients with the tumors in head and neck region after the radiation therapy

Indices	Norm	Groups of patients			
		Control (n=20)		Basic (n=22)	
		Before treatment	1 month after treatment	Before treatment	1 month after treatment
MDA, mcmol/l	0.27±0.02	0.46±0.05	0.40±0.03	0.40±0.02	0.30±0.03
I					
I ₁		<0.05	<0.05	<0.05	>0.05
I _c			>0.05		<0.05
					<0.05
Activity of catalase mcat/l	0.42±0.06	0.22±0.02	0.30±0.03	0.28±0.03	0.38±0.02
I					
I ₁			<0.05	<0.05	>0.05
I _c			<0.05		<0.05
					<0.05
API	1.55	0.48	0.75	0.70	1.26

Note: I — index of reliability of differences with group “norm”; I₁ — index of reliability of differences with group “before treatment”; I_c — index of reliability of differences with the “control” group.

The conducted biochemical analysis of oral fluid in patients revealed the decline of MDA inflammation marker with topical application of “Apior” gel on average from (0.40±0.02) mcmol/l to (0.30±0.03) mcmol/l, in the control group this index was higher (Table 4). The local application of gel, lowering processes of peroxidation caused by irradiation in OM tissues, resulted in activation of protective enzymes of the antioxidant system in the oral fluid. Level of activity K in the basic group patients increased by the end of treatment up to the normal values, which indicated the antioxidant properties of the new gel, the control group patients had reduced K activity. Corresponding with the treatment of antioxidant-prooxidant index heightened, the application of “Apior” more pronounced than in the control group.

Using local application of the new hygienic agent in complex therapy of oncologic patients exposed to radiation therapy, it showed restored cytokine balance in the blood serum. The patients exposed to the total boost dose (TBD) of radiation 40 Gy, the pro-inflammatory cytokines IL-6 concentrations increased on average 2.0 and 2.5 times in comparison with the level before and after the irradiation; anti-inflammatory cytokine IL-4 concentration increased on average 1.5 times (Table 5). The treatment with the use “Apior” gel facilitated inhibition of developed cytokine output, which was shown by IL-1 decline on average by 26.3 %, IL-6 — by 58.2 % as compared with the figures before treatment and increase of anti-inflammatory

cytokine IL-4 level by 46.2 %. In the control group patients, traditional therapy had less pronounced influence in the level of studied cytokines.

Oncologic patients after the radiation therapy with TBD 60 Gy the level of SIgA in the oral fluid fell down 2 times as compared with that one before irradiation, which is evidence of postradiation violation of oral immunity. Topical application of the new medication for oral care facilitated recovery of secretory immunoglobulin in the oral fluid. In the patients having only routine treatment the SIgA level in the oral fluid averaged (0.56±0.03) g/l by the end of treatment, which was 1.5 times lower than before irradiation, “Apior” gel application in the patients of basic group allowed to restore its level up to initial value (Table 6).

Microbiological examination of oral fluid of oncologic patients after the radiation therapy revealed that the average value of microbial contamination made (4.82±0.41) lg CFU/ml was much higher than in the control subjects (2.10±0.34) lg CFU/ml). Microbial level of patients of examined groups was characterized by reduction of isolation rate of representatives of resident stabilizing flora. The appeared ecological niche was filled with conditional-pathogenic and pathogenic bacteria, the number of which multiplied. A decline of Streptococcaceae and Lactobacterium isolation on average by 18 %, at the same time there was a rise of Micrococcus luteus. Among the gram-positive coccal flora, there was a number of

Staphylococci, Enterobacteriaceae representatives, as well as Klebsiellae and Escherichiae. *Candida albicans* fungi was revealed in a great number of patients (48 %). A rule 5–6 types bacteria association were present.

Table 5. Level of pro- and anti-inflammatory cytokines in the peripheral blood of oncologic patients, exposed to radiation therapy during treatment of radioreactions in the oral cavity

	Before irradiation	Groups of patients			
		Control (n=8)		Basic (n=10)	
		before treatment	after treatment	before treatment	after treatment
IL-1	46.4±3.4	90.8±8.2	78.8±9.2	84.6±7.2	62.4±5.8
I ₁		<0.05	<0.05	<0.05	<0.05
Ic			>0.05		>0.05
IL-6	26.8±2.1	67.6±6.0	48.7±4.2	72.4±7.1	30.3±4.2
I ₁		<0.05	<0.05	<0.05	>0.05
Ic			<0.05		<0.05
IL-4	24.2±2.8	38.6±5.8	48.4±6.1	40.6±6.3	58.8±6.2
I ₁		<0.05	<0.05	<0.05	<0.05
Ic			>0.05		<0.05
					>0.05

Note: I — index of reliability of differences “before irradiation”; I₁ — index of reliability of differences “before treatment”; Ic — index of reliability of differences with the “control” group.

The analysis of microflora of oral fluid after the traditional treatment revealed reduction of isolation rate of both pathogenic, conditional-pathogenic kinds and representatives of normal microflora. The patients with topical application of “Apior” gel, against a background of considerable decline of pathogenic and

conditional-pathogenic strains the per cent of resident flora Streptococcaceae and *Lactobacterium rose*. After the conducted course of treatment, a decline of the mean level of microbial oral bacterization was marked, both in basic, and in the group of comparison up to (2.55±0.68) lg CFU/ml and 3.10±0.13 lg CFU/ml correspondingly.

Application of “Apior” gel facilitated microbiocenosis stabilization in the oral cavity of oncologic patients: bacterial rate decreased 1.5 times, and *Candida* fungi — 2 times. The greatest antimicrobial activity of “Apior” was marked in relation to enterobacteria (bacterization — 50 %) and non-hemolytic streptococcus (40 %).

Consequently, the application of “Apior” gel in the complex therapy of radiation complications in the oral cavity in patients with the tumors in head and neck region after conducting radiation therapy was instrumental in the substantial decline of pronouncement of manifestations of radioreactions and rapid alleviation. As compared with other patients who had a traditional anti-inflammatory therapy, the patients who had a combined treatment including topical application of apigel were observed a decline of oral edema and erosions, rarer bleeding of gums, phenomena of confluent and focal epithelitis, ulcerous processes. More rapid reduction of xerostomia pronouncement was observed, which was instrumental in the improvement of hygienic state of oral cavity; prevention of the secondary microbial colonization of damaged mucous surface. The biochemical analysis of oral fluid in patients showed that the application of gel prevented the outbreak of lipid peroxidation, inflammations in OM tissues, stimulates activity of antioxidant enzymes, which improves nonspecific resistance in the oral cavity.

Table 6. Influence of gel on secretory immunoglobulin A level in the oral fluid of patients exposed to X-ray therapy of TBD 60 Gy, g/l

Index	Before irradiation	Groups of patients			
		Control (n=8)		Basic (n=10)	
		before treatment	in 1 month after treatment	before treatment	in 1 month after treatment
SigA	0.81±0.05	0.42±0.03	0.56±0.03	0.48±0.04	0.69±0.03
I ₁		<0.05	<0.05	<0.05	<0.05
Ic			<0.05		<0.05

Note: I — index of reliability of differences “before irradiation”; I₁ — index of reliability of differences “before treatment”; Ic — index of reliability of differences with the “control” group.

The comparative estimation of obtained data allowed us to make a conclusion that the extent of manifestation of radioreactions depends on imbalance of spectrum pro- and anti-inflammatory cytokines with the primary production of anti-inflammatory cytokines. Such changes of cytokine balance in blood of oncologic patients belong to important pathogenic mechanisms of inflammation and cancerogenesis development [15]. So, topical therapy of “Apior” gel is a proved component of complex treatment of OM radioreactions, which helps activating local immunity as well as possibly to improve ability of tissues for protection against infection and restore OM microbiocenosis balance after the radiation therapy.

The analysis of results showed that the application of “Apior” gel in the complex treatment of radiation complications in the oral cavity had healthy influence on quality of life of patients with the tumors in head and neck region after the radiation therapy and reduction of their rehabilitation term.

This study indicated advisability of the developed gel “Apior” as a curative-preventive mean with treatment of radiation complications in the oral cavity after conducted radiation therapy in oncologic patients with the tumors in head and neck region for improvement of quality of life and level of rehabilitation.

Conclusion

1. The topical application of “Apior” gel in the complex therapy of radiation complications in the oral cavity in patients with tumors of head and neck region undergoing radiation treatment subside pronouncement of symptoms of xerostomia and OM radioreactions.

2. The new apigel improves hygienic state of oral cavity, salivation, positively affects nonspecific resistance of oral fluid, rendering a radioprotective action.

3. A positive effect of the local application of new curative-preventive mean is reached due to renewal of balance of pro- and antioxidant activity, reduction of level of pro-inflammatory (IL-1, IL-6) and rise of anti-inflammatory (IL-4) cytokines, restoration of secretory immunoglobulin A, normalizes oral microbiocenosis.

4. The Apior gel has antimicrobial activity: reduced 1.5 folds of the pathogenic and conditionally-pathogenic strains, 2 folds the *Candida* fungi in the oral fluid of oncology patients after the radial therapy.

Conflict of Interest

There is no conflict of interest

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