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Diagnosis and treatment of radiation-induced xerostomia

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Abstract. The purpose of the study was to improve diagnostic approaches and treatment protocols for patients with various forms of xerostomia, including reactive dystrophic changes and radiation-induced lesions of the salivary glands. 64 patients aged 31 to 92 years, divided into two groups, were diagnosed and treated. The Group 1 (n = 33) included patients with salivary gland diseases (sialadenosis, chronic mumps, Sjögren's syndrome) that developed against the background of concomitant somatic pathology. The Group 2 (n = 31) consisted of patients with radiation-induced xerostomia after radioiodine therapy and remote irradiation for tumours of the maxillofacial region. The diagnosis included dynamic subtraction sialography, sialometry of the large and small salivary glands, analysis of the viscosity and pH of secretions, and biopsy of the small salivary glands. Patients in the Group 1 underwent external blockades according to Vishnevsky with 0.5% procaine solution and 1% Mexidol, injections of 1% galantamine hydrochloride solution, administration of 2-5% potassium iodide solution and compresses with Dimexide. In Group 2, modern salt substitutes (Bioten, Hiposalix, and Xerostom complexes) were prescribed in the form of gels, sprays, chewing gum, etc. Clinical improvement was observed in 22 patients (66.7%) of the Group 1. In Group 2, where the secretion indices were significantly reduced (to 0.1-0.3 ml), the pH of saliva shifted to the acidic side (5.0-6.0), and the viscosity of the secretion reached 12 cm, only 5 people (16%) reported relief of symptoms. Treatment of xerostomia requires a comprehensive, multidisciplinary approach. Due to the irreversible destruction of acinar tissue and fibrosis, restoration of saliva secretion in radiation damage is impossible, and therefore permanent replacement therapy and preventive oral sanitation before starting radiation treatment are priorities

Keywords: salivation disorders; hyposecretory conditions of the salivary glands; post-radiation lesions; saliva replacement therapy; radiopaque examination of salivary ducts

Introduction

Xerostomia (dry mouth) is diagnosed in patients with various diseases of the salivary glands (SG) and concomitant pathologies. Xerostomia occurs in various diseases of the gastrointestinal tract, genitourinary and endocrine systems, rheumatological and neuroendocrine diseases, and autoimmune conditions. According to V.V. Afanasyev, xerostomia develops against the background of taking medications (23%), thyroid diseases (17%), nervous system diseases (17%), type 2 diabetes (12%), hypogonadism (7%), Sjögren's syndrome (13%), and radioiodine therapy (3%) [1,2]. Oral dryness develops in patients with malignant diseases of

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the maxillofacial region (MFR) after combination therapy. The number of patients with malignant diseases of the MFR is steadily increasing. The increase in such patients was 1.2% compared to 2017. The treatment of tumours of the maxillofacial region was combined, including surgical, chemo and radiation treatment, and their combination. Radiation therapy often plays a leading role in treatment. This is caused by several factors: the elderly age of patients, the inoperable nature of the tumour process due to its prevalence and the presence of severe concomitant pathology.

During radiotherapy, the entire tumour and adjacent healthy tissues (skin, mucous membrane of the oral cavity and pharynx, salivary glands, teeth, bones) are irradiated. Radiation therapy is based on damage to the DNA of cells, resulting in mitotic and interphase cell death [3,4]. The effects of ionising radiation on body tissues are divided into radiation reactions and radiation damage. Local radiation reactions occur in all patients and are reversible after adequate complex treatment [5]. These include: epitheliitis (mucositis), loss of taste sensations, and oral infections. Radiation injuries (complications) occur when treatment planning is disrupted, the radiation dose is exceeded, and there is no protective equipment. These include: trismus, radial caries, radiation ulcer, xerostomia, and osteoradionecrosis of the jaws. The salivary glands have a low tolerance to radiation, and during radiotherapy for the MFR tumours, they are almost always within the direct radiation beam. The reaction to radiation appears after a total focal dose of 10 Gy [6]. With an increase in the radiation dose, inflammatory processes in the parenchyma of the gland increase and, with a cumulative focal dose (CFD) of 50-60 Gy, lead to irreversible consequences in SG, which is manifested by severe fibrosis and atrophy of glandular tissue with impaired excretory function [7]. Radiation-induced xerostomia in patients with malignant diseases of the head and neck is observed in 80% of cases and significantly worsens the quality of life. A.D. Getman examined 68 cancer patients after radiation therapy and found that women (55.88%) are more likely to suffer from xerostomia than men (41.12%). Patients reported burning of the oral mucosa (32.35%) and pain in the salivary glands (19.12%) [8].

A decrease in salivation causes discomfort during communication, increases the risk of developing psychoemotional disorders, disrupts the digestive process, and leads to diseases of the gastrointestinal tract (gastrointestinal tract), tooth decay develops, periodontal diseases worsen. These factors lead to the need for early surgical interventions in patients after radiation therapy with the possibility of developing a serious complication – osteoradionecrosis of the jaw and radiation ulcer. Radioactive iodine therapy has been used in clinical practice since the 1940s for the non-invasive treatment of thyroid diseases. A common secondary complication of treatment is damage to the salivary glands with the development of sialadenitis and xerostomia. The therapeutic effect of radioactive iodine is obtained by beta rays, which cause direct and indirect damage to cells. After administration, it is concentrated in the SG with the development of an inflammatory reaction, with infiltration and narrowing of the ducts and the development of a "salivary plug". This leads to an increase in oedema and an increase in periductal pressure. Depending on the anatomical structure of the secreted secretions, the parotid salivary glands are most sensitive to radioactive iodine, compared with the submandibular and salivary glands. SG dysfunction develops as a result of fibrous changes followed by loss of secretory cells [9]. Clinically, this is manifested in enlargement and pain of the parotid salivary gland, as a result of obstruction of the duct by a "salivary" plug. After eating, under the influence of the secretion current, the obstruction passes, and the salivary gland calms down. Symptoms may appear immediately after administration of the therapeutic dose of I–131 or after several months, and their intensity will increase over time.

Patients with radiation-induced xerostomia complain of dry mouth, pain in the digestive tract, burning sensation of the oral mucosa, bad breath, deterioration of diction and sonority of voice, development of dysgeusia [10]. Timely treatment and prevention will help patients to socialise after suffering from serious illnesses. Patients with SG pathology, including those with xerostomia, are subject to mandatory follow-up and routine oral sanitation [11]. First of all, before treatment, all patients should be informed about potential complications and preventive measures to reduce negative effects. During radioiodine therapy, lemon juice, sour sweets, and drinking plenty of fluids are used to stimulate salivation and reduce the time taken for I–131 to be excreted via the excretory system (gustatory and mechanical stimulation of salivation). Massage of the parotid salivary gland is also effective for the rapid elimination of accumulated radioactive iodine.

Therapy of patients with xerostomia, especially radiation-induced xerostomia, is symptomatic and is limited to the use of artificial saliva. Its use causes a short-term feeling of moisture. A long-used and well-studied drug is pilocarpine hydrochloride [12]. But its use can lead to undesirable consequences. Treatment of radiation-induced xerostomia is very difficult and should be coordinated with doctors of other specialities, since its cause is combination therapy of malignant diseases of the head and neck. In this study, patients with radiation-induced xerostomia were examined, diagnosed, and treated. The purpose of the study was to improve the methods of diagnosis and treatment of patients with various forms of xerostomia.

Materials and Methods

A comparative study of the effectiveness of diagnosis and treatment of patients with xerostomia developed

against the background of various somatic diseases has been conducted. When completing medical documentation, all patients signed informed voluntary consent for preliminary examination, consultation and treatment, and consent to the processing and transfer of personal data and information constituting a medical secret. The documentation was prepared at the clinical centre of the Department of Maxillofacial Surgery and Traumatology at the Russian University of Medicine, a Federal State Budgetary Educational Institution of Higher Education under the Ministry of Health of Russia. The total number of examined patients was 64, divided into two groups. The Group 1 included 33 patients with salivary gland diseases with concomitant pathology: sialoadenosis was diagnosed in 24 patients, chronic mumps in 6, Sjögren's syndrome in 2, galvanosis in 1. The Group 2 included 31 patients with radiation-induced xerostomia: 15 patients after radioiodine therapy, 15 patients after radiation therapy, among whom 13 patients had osteoarthritis of the jaw, and 1 patient had myeloma.

The age of the examined ranged from 31 to 92 years. All patients underwent general and special examination methods. This study was performed in accordance with the international principles of the World Medical Association [13]. The main complaints were dryness of the oral cavity, which worsens at night, sleep disorders associated with the need to moisten the oral cavity, long-term non-healing angular cheilitis, burning of the oral mucosa, difficulty speaking and eating, tongue sticking to the palate, an unpleasant taste in the mouth, frequent traumatisation of the mucous membrane of the lips and cheeks. There was also a salty or sour taste in the mouth, emotional lability with a predominance of tearfulness. The quality of life of patients was reduced. The duration of the complaints ranged from 6 months or more.

Examination of patients with salivary gland diseases included general clinical methods: medical history collection, examination, palpation, laboratory blood and urine tests. Examination and palpation revealed soreness, enlargement of the salivary glands, changes in their consistency, and the presence of intragastric lymph nodes. Examination of the oral cavity assessed the condition of the mucous membrane of the lips, cheeks and vestibule of the oral cavity, and the nature and consistency of secretions from the mouths of the salivary glands. Special research methods included probing the salivary gland ducts, radiography of the salivary gland area, sialography, sialometry, and qualitative analysis of secretions (colour, transparency, presence of inclusions). Additionally, computed sialotomography, dynamic subtraction sialography, and biopsy of the small salivary glands were used. Stimulated sialometry of the large and small salivary glands, determination of saliva pH, and assessment of secretion viscosity were performed [14].

Sialometry was performed using two methods. The first method (T.B. Andreeva), involving duct occlusion using a plastic catheter, was used in all 64 patients for the functional assessment of the salivary glands. The second method using the Leshley-Yushchenko-Krasnogorsky capsule was used in 35 patients as a repeat study with increased secretion viscosity [15]. The study was conducted in the morning on an empty stomach. 30 minutes before the catheter was inserted, 8 drops of 1% pilocarpine hydrochloride solution were administered orally. After inserting the catheter into the salivary duct, the secretion was collected in a graduated tube for 20 minutes, followed by an assessment of the amount, transparency and viscosity. Additionally, mixed saliva was collected in a graduated tube for 10 minutes. Sialometry of the small salivary glands was performed by counting the functioning small salivary glands on the mucous membrane of the lower lip within a 2x2 cm frame (Fig. 1).



Figure 1. Application a frame and counting the number of secreted drops of small salivary glands
Source: created by the authors

In the absence of contraindications, sialography was performed using water-soluble contrast agents. Solutions of Omnipack, Unigexole, and Ultravist were used to contrast SG (Fig. 2).

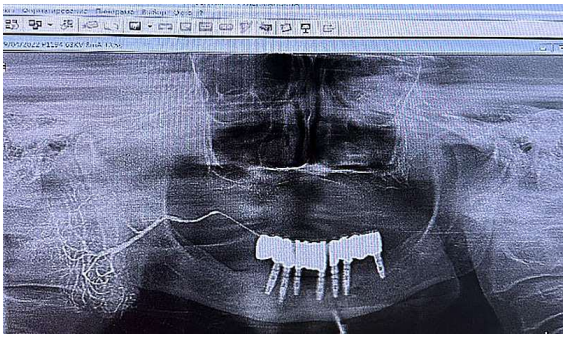


Figure 2. Sialogram of patient R., born in 1950, diagnosis: sialadenosis on the background of radioiodine therapy
Source: created by the authors

The state of the ductal system was determined: the clarity of the contours of the ducts, the expansion or narrowing of the main duct, the expansion or narrowing of the ducts of 1-5 orders, the displacement of the ducts and their intermittency (Fig. 3).

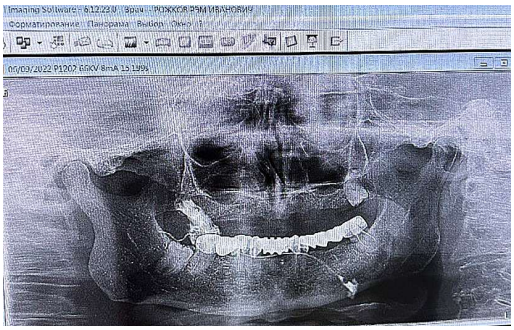


Figure 3. Sialogram of patient R., born in 1933, diagnosis: sialadenosis on the background of combination therapy
Source: created by the authors

To study the parenchyma, the image quality, the presence of filling defects, the presence of cavities, their diameter and clarity were evaluated (Fig. 4).

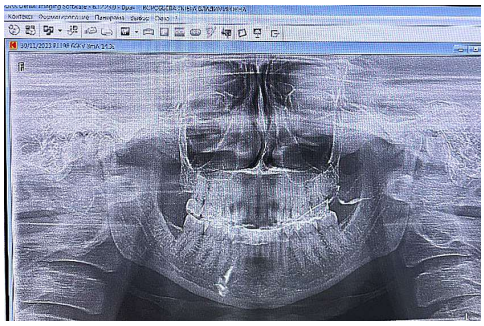


Figure 4. Sialogram of patient V., born in 1970, diagnosis: radiation-induced xerostomia on the background of radioiodine therapy
Source: created by the authors

The patients underwent oral sanitation, and, if necessary, a referral was made for consultation and treatment with an orthopedic dentist for the purpose of rational prosthetics. They were also referred for consultations and treatment to other specialists: gastroenterologist, gynecologist, urologist, endocrinologist. Blood and urine tests were performed. All patients were provided with an information leaflet developed by the Department of Maxillofacial Surgery and Traumatology outlining recommendations for the management of xerostomia. It was recommended to drink plenty of fluids; sedatives were prescribed, along with motherwort tincture, 30-40 drops three times a day for 2-3 months. The leaflet provided recommendations on the use of saline substitutes to eliminate dry mouth.

The saliva acidity was determined using special diagnostic test strips. With a normal hydrogen index of 6.8-7.0 pH, patients with radiation-induced xerostomia had apH of 5.0-6.0, i.e., an acidic reaction, which worsened the condition of the oral cavity and caused discomfort in patients. To determine the viscosity, the method of stretching a drop of secretion on the branches of tweezers was used, which was accessible to all doctors. Normally, saliva can stretch up to 1.0 cm. The number of centimetres was recorded in the medical history. In patients, the viscosity ranged from 2 to 12 cm. There is a special device for measuring viscosity, the so-called viscometer. But for its objective operation, at least 5 ml of the secret is needed. In patients, such an amount cannot be obtained even with stimulated secretions. Patients of the Group 1, who had xerostomia on the background of general somatic diseases, were prescribed external blockages with 0.5% procaine solution with 1% Mexidol solution from 20 to 40 ml of the solution. The frequency of manipulations was 3-5 injections per salivary gland. The blockades were repeated after 2-3 days. Most often, injections were performed on both glands, alternating them. Their action was aimed at improving the trophism and increasing the function of the salivary glands (Fig. 5).



Figure 5. echniques for performing external nerve blocks, positioning of the patient and the doctor
Source: created by the authors

Subcutaneous injections of 1% galantamine hydrochloride solution, subcutaneously 1 ml, for 1 month were also prescribed. Patients were prescribed a 2-5% solution of potassium iodide to be taken orally, 1 tablespoon three times a day, washed down with milk. At home, patients were prescribed compresses on the SG area with a 30% Dimexide solution. The administration of blockades and subcutaneous injections to patients of Group 2 with radiation-induced xerostomia had its own limitations. The drugs were administered after consultation with the attending oncologist. As a

result, blockages were performed in 5 patients after radioiodine therapy, which was 16%, and in 1 patient after combination therapy without osteoarthritis (3%). Patients with radiation-induced xerostomia underwent local and general treatment after combined treatment with osteoradionecrosis of the jaw: treatment of purulent wounds with antiseptic solutions, enzymes and anti-inflammatory ointment applications, detoxification treatment, hyperbaric oxygenation (HBO). Only artificial saliva was prescribed to alleviate xerostomia. Patients of the 2 groups were prescribed saline substitutes in the form of gels, sprays, chewing gum, etc., for palliative treatment. They provided protection for the oral mucosa, facilitated speech, food intake, and prevented the development of tooth decay. These included Bioten (USA), Hiposalix (France), Xerostom (Spain), etc.

Results

Treatment of xerostomia presents great difficulties. This is primarily conditioned by the fact that it is necessary to find out the cause of the development of such a condition. Methods and means were used to improve the trophism and function of the SG. The dryness of the oral cavity in patients of groups 1 and 2 was constant and its clinical signs were of the same type: the mucous membrane was pale pink, slightly moistened, and the spatula stuck to the tongue and cheeks. A large amount of easily removable plaque was found on the back of the tongue. There was a small amount or absence of free saliva in the sublingual area. The viscosity of saliva was significantly higher than normal: up to 8 cm (normally up to 1 cm). When LV was massaged, a secret in the form of a medium or large drop was released from the mouths of the ducts and lingered near the mouth. In patients with Sjögren's syndrome and radiation-induced xerostomia, the first portions of the secretion resembled a cloudy gel-like mass, a "salivary" plug.

In Group 1 (33 people), according to sialometry data, 31 patients with interstitial sialadenosis and chronic mumps had normal secretions: 0.8-1.2 ml. Two patients with SS had a significantly marked decrease in SG secretion: 0.1-0.5 ml. In patients of Group 2 (31 people) with radiation-induced xerostomia, sialometry data showed a significant decrease in secretions: up to 0.1-0.3 ml from major SG, 2-9 drops from minor SG. Patients after radiation therapy subjectively felt less xerostomia, but the objective indicators of secretion were worse. It is believed that this is conditioned by the presence of a severe underlying pathology (osteoradionecrosis), which distracted attention from the dryness of the oral cavity. It is also assumed that the patients were mentally prepared for a difficult condition and mobilised their forces for treatment. Patients after radioiodine therapy, whose secretion state was better, but they felt worse. This is due to the fact that the main complaint, in addition to dry mouth, they noted an increase and swelling in the salivary gland, the so-called obstruction of the ducts of the salivary glands. The follow-up period ranged from 2 to 6 years. Not all patients were able to withstand the schedule of follow-up. After the treatment and improvement, they demonstrated low adherence to treatment (compliance), referring only during periods of exacerbation. This significantly complicated the treatment and reduced the positive dynamics. But those patients who came for outpatient treatment without waiting for complications received a stable and positive result.

After treatment, improvement was noted in patients of Group 1 with pathology of the salivary glands on the background of concomitant pathology. Unpleasant feelings of bursting in the salivary glands became less frequent, and the unpleasant taste of salty or sour food disappeared. The sialometry performed after 6 months showed that 22 patients noted an improvement in the oral cavity. An increase in the level of secretion was noted in 2 (out of 22) patients, which amounted to 9%. In the rest, the increase in secretion levels was not significant. In patients of Group 2 with radiation-induced xerostomia, only 5 patients with sialadenosis were able to achieve a positive result on the background of radioiodine therapy (16%). Repeated sialometry after 6-9 months showed a slight increase in salivary gland secretion to 0.5-0.8 ml, but these data were still below normal. In this group of patients, the use of saline substitutes, the performance of gustatory and mechanical stimulation of secretions played a significant role. Effective moistening of the oral cavity helped to improve the quality of life of patients.

Discussion

The problem of xerostomia, especially its radiation-induced form, remains one of the most difficult tasks of modern maxillofacial surgery and dentistry [16,17]. The present study confirmed the thesis that dry mouth is a multifactorial condition requiring a differentiated diagnostic approach that considers both systemic factors and local damage to the SG parenchyma [18]. During the research, 64 patients were examined. In Group 1 (n = 33), where xerostomia developed against the background of general somatic diseases, clinical improvement was achieved in 66.7% of patients. These data correlate with the conclusions of V.V. Afanasyev [19], indicating that sialadenoses are reactive-dystrophic in nature and with adequate correction of the underlying disease in combination with local stimulating therapy, the function of SG can be partially restored. The use of blockades with Mexidol and procaine, and galantamine injections, was aimed at improving trophic and conduction of nerve impulses, which is consistent with modern protocols for the treatment of hypoxia.

On the contrary, in the second group (radiation-induced xerostomia, n = 31), positive dynamics was observed only in 16% of patients. Such a sharp difference is explained by the irreversible nature of ionising radiation damage. According to X. Li *et al.* [20], SG have

a high radiosensitivity, and when CFD reaches above 50 Gy, degenerative changes occur: acinar necrosis and replacement of parenchyma by fibrous tissue. Special attention should be paid to the subgroup of patients who underwent radioiodine therapy (I–131). The revealed clinical signs – pain and a feeling of bursting in the SG area – are conditioned by a specific mechanism of isotope concentration in serous cells. These findings are consistent with the study by M. Adramerinas & D. Andreadis [21], which described the staging of radioiodine-associated sialadenitis characterised by obstructive symptoms and progressive loss of salivary gland function, and xerostomia, which significantly affects patients' quality of life. The diagnostic stage showed that in radiation patients, the pH of saliva shifts to the acidic side (5.0-6.0), and the viscosity of secretions increases to critical values (12 cm according to the Andreeva method). Similar changes are described as a leading factor in disrupting the processes of self-purification and mineralisation, which leads to the development of "radial caries". The use of Lashley-Yushchenko-Krasnogorsky capsules in this research helped to objectify the degree of hypofunction when standard sialometry was difficult due to the viscosity of the secretion.

An analysis of therapeutic approaches has shown that the possibilities of drug stimulation in radiation damage are extremely limited. Although pilocarpine remains the preferred method of stimulation, its systemic effects are often poorly tolerated by patients. But its long-term use has side effects (headaches, palpitations) and is contraindicated in glaucoma, bronchial asthma, chronic obstructive pulmonary disease, and cardiovascular diseases. Therefore, prescribing it to patients with xerostomia is not recommended. The saline substitutes used provided temporary hydration and improved quality of life, but their effect remained palliative. M.S. Hosseini *et al.* [6] indicated that various drugs and methods have been proposed for the treatment of this disease, including salivation substitutes and stimulants, muscarinic agonists, antitumour, detoxifying agents, etc. They recommended using clinical guidelines for doctors, which allow for an individual approach to the treatment of xerostomia. Thus, the results of the study emphasise the need for a preventive strategy. Interdisciplinary collaboration between oncologists and dentists, the use of radioprotectors and sialoprotection agents at the radiation stage are the only effective ways to minimise the risk of irreversible xerostomia.

Conclusions

Radiation-induced xerostomia on the background of radiation therapy and radioiodine therapy in patients with malignant tumours of the MFR and thyroid cancer presents great difficulties. Contemporary treatment methods cannot completely solve this problem effectively. Thus, the results of the study indicate the need for an integrated approach to the treatment of sialadenosis, including a general effect on the body and local therapy of the salivary glands, which together ensures the achievement of a sustained therapeutic effect. In radiation-induced xerostomia, the use of saline substitutes plays an important role, helping to reduce the severity of dryness of the oral cavity and maintain adequate hydration of the mucous membrane. However, complete restoration of salivation in this category of patients is not possible due to irreversible loss of acinar tissue. Before carrying out combined treatment of malignant neoplasms and radioiodine therapy, it is advisable to implement preventive measures, including oral sanitation, informing patients about possible complications and training in ways to prevent and correct them. The organisation of interdisciplinary interaction at all stages of patient management contributes to a significant reduction in the risk of developing xerostomia and other radiation lesions of the maxillofacial region.

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Conflict of Interest

None.

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