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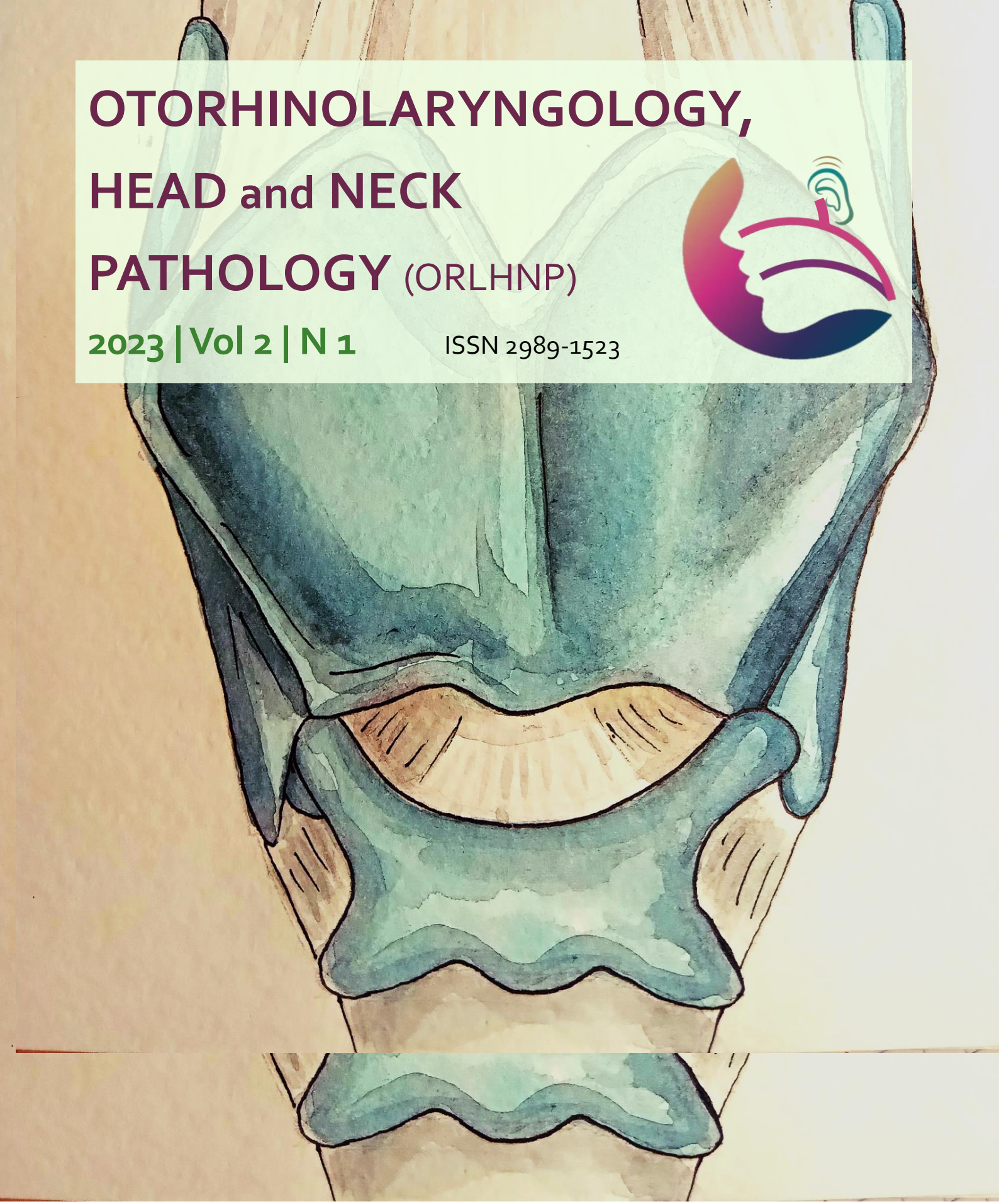

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Contents

Article

The Influence of medical and social factors on the incidence of nasal cavity and paranasal sinuses.

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Abstract: the statue is about the effect of medical and social factors on the development of nasal cavity and paranasal sinuses diseases, the degree of patient's satisfaction with the medical care provided, and the analyzed approaches to patients care in prehospital and hospitals treatment.

Keywords: the nasal cavity and paranasal sinuses diseases, specialized medical care, medical and social characteristics of patients.

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1. Introduction

In the general structure of the ENT organs diseases, the pathology of the nasal cavity (NC) and paranasal sinuses (PNS) in recent years has firmly taken first place both among outpatients and in the group of patients undergoing inpatient treatment [1,2].

Currently, one of the priorities is to develop measures to improve the provision of medical care to patients in hospitals for NC and PNS at outpatient and inpatient faculties, taking into account the incidence of this pathology and the identified socio-economic and hygienic characteristics of the behavior of this group of patients, which predetermined the practical the feasibility of this study [3,4].

The aim of the work is to analyze the influence of medical and social factors on the development of NC and PNS diseases and the effectiveness of the treatment of this pathology in outpatient and inpatient institutions [5].

2. Patients and Methods

The study was carried out in several stages. At the first stage (from 2007 to 2011), an analysis was made of the hospitalized morbidity of patients with pathology of ENT organs in the ENT department of the SBHI "City Clinical Hospital No. 4" of the Moscow DH and an analysis of the work of ENT rooms of outpatient institution of the SWD of Moscow by studying the summary annual reports of the district otorhinolaryngologist on the incidence of the adult population and clinical examination [6,7]. *(Fig. 1.)*.

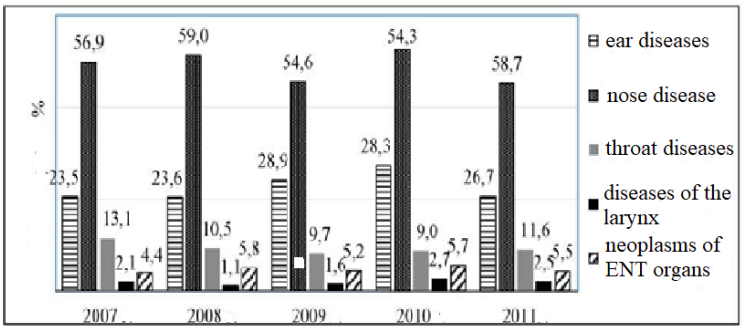

Figure 1. The structure of hospitalized morbidity of ENT organs in 2007-2011

The second stage (2012-2013) is based on the analysis results of a survey of 400 patients with nasal cavity and paranasal sinuses diseases who were hospitalized in the ENT Department of the City Clinical Hospital No.4 SBHI SP No. 68 DHM branch No. 1 CAD of Moscow social and hygienic characteristics, age and sex characteristics of the examined, the moral and psychological

climate in the family, satisfaction with the medical care provided, patient awareness of medical services were studied (questionnaire of a selective group of patients) [8,9].

To implement the second stage, the Department of Otorhinolaryngology, together with the Department of Public Health, Healthcare and Hygiene, of the Federal State Autonomous Educational Institution of Higher Education "Peoples' Friendship University of Russia" developed two types of questionnaires for a comprehensive medical and social characteristic of the treatment and diagnostic process in the clinic, hospital and family health.

The questionnaires consist of two parts:

1. Comprehensive medical and social characteristics of the treatment and diagnostic process in a hospital (city clinic) and family health. This part of the questionnaires was filled in by the patients themselves (questionnaire for the hospital - 47 questions, for the polyclinic - 38 questions).

2. A map of copying information from the medical history (outpatient card) and an expert assessment of the organization and quality of medical care for the patient (19 questions for the hospital and 15 questions for the polyclinic).

The card contains information related to a specific disease with which the patient was treated by a polyclinic ENT doctor or in a hospital, which allows, at the third stage of the study, to evaluate: the quality of the examination, the quality of the treatment (volume, timing, combination of treatment methods, duration) , the outcome of the disease, the duration of the general temporary disability. The final stage included the development of measures to improve medical care for patients with NC and PNS diseases at the outpatient and inpatient levels, taking into account the incidence of this type of pathology and the identified medical and social characteristics of this group of patients.

3. Results

In exceptional cases of the nose and paranasal sinuses diseases, purulent paranasal sinuses diseases prevailed: acute sinusitis 32.0% and chronic sinusitis - 25.0% (average over 5 years). In second place, by choice, were the curvature of the nasal septum - 19.0%, nose and paranasal sinuses diseases - 7.0%, boils, nasal abscesses and other skin disease and subcutaneous tissue - 7.0%, rhinitis (all forms) - 6%, nosebleeds - 2%.

When analyzing the incidence according to the statistical reports of the SWD of Moscow, it was revealed that diseases of the pharynx were in the first place - an average of 26,531 cases per year (38.8%), and NC and PNS diseases were in second place - 19,146 cases per year (28.0%), diseases of the ear - 17520 cases (25.6%) and larynx - 5192 cases per year (7.6%) (Fig. 1.).

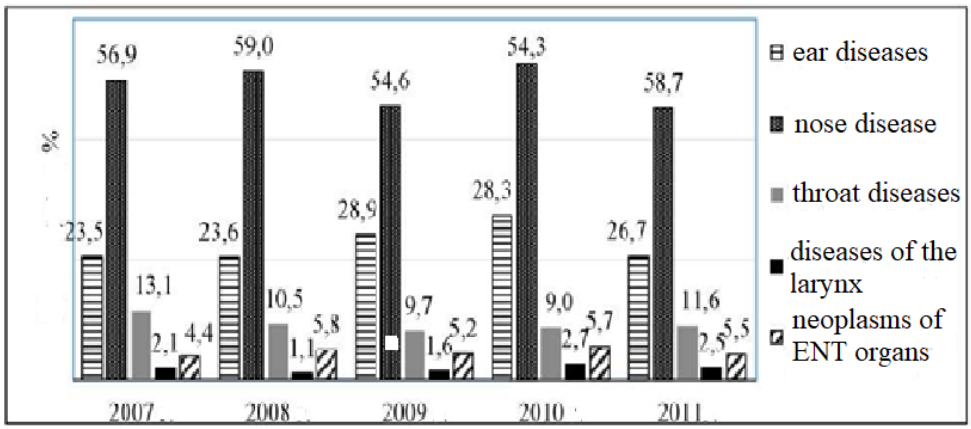

Figure 1. Morbidity of the attached population according to the data of appeals to outpatient clinics of the district for 2007-2011

Among the isolated diseases of the nose and paranasal sinuses, acute rhinitis prevailed - in 6479.8 cases, which was detected33.9% of all infections with the NC and PNS diseases, chronic rhinitis - 4173.6 (21.8%), acute sinusitis - 3332.8 (17.4%).

If we consider the number of visits for each year of the study, then the largest number of visits with nasal cavity and paranasal sinuses diseases (19728 people) and the pharynx (26865

people) occurred in 2008, with ear pathology - in 2007 (19080 people), larynx - in 2009 (5846 people).

The first place in the structure of the temporary loss cause was occupied by acute ENT organs pathologies, among which the share of ear pathologies and mastoid process was 31.3-33.1%, the nasal cavity and paranasal sinuses - 29.5-30.3%, pharyngeal cavity - 24.1-24.6%. Chronic the ENT organ's diseases in terms of disability case number occupied the second place in the structure of temporary disability causes. In this group, the nasal cavity and paranasal sinuses diseases were in the lead - 41.4 (42.2%), pharynx - 29.1 (30.2%), ear and mastoid process - 18.6 (19.6%). In general, despite the decrease in the total cases number of disability from 2007 to 2011, the number of days of disability remained practically unchanged due to an increase in the average duration of the disease from 9.5 to 9.7 days.

According to the study, the treatment duration of patients with nasal cavity and paranasal sinuses diseases at the outpatient stage varies from 5 to 65 days - 7 days (21%), 10 days (18.5%), 14 days (12.8%). The number of days of temporary disability (TD) varied from 5 to 14 days - 7 days of TD in 81.4% of cases, no more than 7 days of TD - 89.2%, no more than 9 days of TD - 92.3%.

Out of 400 inpatients, 53.5% were hospitalized as planned by the polyclinic, 29.5% were urgently hospitalized by the polyclinic, 9.8% by emergency medical care, and 7.0% independently. The period from the onset of the disease to hospitalization , allows us to divide patients into 3 groups: the first - these are patients hospitalized within 1 month after the onset of the disease (51.2%; the second - hospitalized within 1 month to 1 year - 7.8% , the third - hospitalized later than 1 year from the onset of the disease - 41.0.

The average number of days after the onset of the disease until the moment of hospitalization (up to 1 month, long periods - months and years are not considered) is 7.6 ± 5.2 days and varies from 1 to 30 days. The period of hospitalization, equal to 7 days, is 21.6%, 10 days - 16.5%, 5 days - 14.6%, 3 days - 8.0%.

Surgical intervention was performed in 97.0% of patients, including 56.3% on the first day, 40.0% on the second.The average number of days elapsed from the moment of hospitalization to surgery is 1.4 ± 0.7 days in the range from 1 to 8.

The total length of stay in the hospital is 7.9±1.6 days (from 2 to 16 days), the duration of the diagnostic period is 1.0±0.0, the treatment period is 7.3±1.8 days (from 1 to 16 days). Recovery occurred in 73.7%, improvement - in 26.0%, no change - in 0.3%. The total length of stay in the hospital for recovered patients is 7.7 ± 1.2 days, with improvement - 8.3 ± 2.5; the duration of treatment for recovered patients is 7.2±1.3 days, with improvement - 7.8±2.6.

Inequality in respondents' assessment of their health manifests itself in the analysis of various socio-economic indicators, such as education, professional level, income, ownership, wealth, etc. According to our study, 14.2% of respondents rated their health as "excellent", 41.8% as "good", 35.9% as "satisfactory", 6.6% as "bad", and "very bad" – 0.1%. Among polyclinic patients, the share of those who rate their health as "excellent" is 3.2 (21.8%) times higher than among hospital patients (6.8%).

Patients with higher education generally rate their health higher (p=0.002). Among them, there are a few more who rate their health as "excellent" (13% versus 11%). This trend is more pronounced in assessing health as "good" (45.2% of people with higher education versus 32.2% of people with secondary education and 39.0% of people with secondary specialized education).

The level of education of respondents is also related to the assessment of their family members health. It has been established that with an increase in education level of the respondent, the proportion of families where all its members are healthy increases linearly by almost 10% from 60.9% for respondents with secondary education and up to 70.7% for those with higher education.

The distribution of respondents with different social status according to their families health (p=0.000) shows that students are the most prosperous from this point of view. Especially in this social group the largest proportion of people with healthy families is noted (92%), in contrast, the ranked series ends with a minimum level - 34.6% of pensioners with healthy families. It is natural that pensioners more often than others note the presence of chronic patients in families (29.9%) against representatives of small businesses (0%), students (1.8%) and intellectuals (1.9%).

The family's health and the patient's health can be attributed to the phenomenon that are interrelated and mutually influencing, when it is difficult to identify the cause and effect. Thus, the relationship between the fact that the respondent is being treated in a polyclinic or in a hospital and the family's health is significant. However, the most eye-catching fact is the following: in healthy families, 51% are outpatients, 49% are inpatients (the distribution is almost equal); more

than half, namely, 67.3% of respondents are treated in a hospital if there are alcoholics or drug addicts in the families and 58.2% - if family members are often sick; but with chronic patients in families, only 31.9% are treated in a hospital. It follows that social and medical problems in the family make patients more likely than in healthy families to resort to inpatient care; the presence of chronic patients, on the contrary, forces the patient to avoid hospitalization, remaining in the family, and use polyclinic medical care.

The ranking of the causes that caused the nasal cavity and paranasal sinuses disease at the moment made it possible to identify the leading ones among them (Fig. 3): the state of the environment and neuropsychic stress are absolutely in the lead - they were indicated by almost 52% and 27% of respondents, respectively. In third place (17%) a complex of external causes, including medical ones, among which injuries, operations, medications, allergic reactions, dental treatment and weather are indicated. Unfavorable working conditions as the disease's cause were emphasized by about 15% of respondents. The least significant causes of diseases are smoking and alcohol (2.8%), living conditions (2.9%) and diet (3.3%).(Fig. 2.).

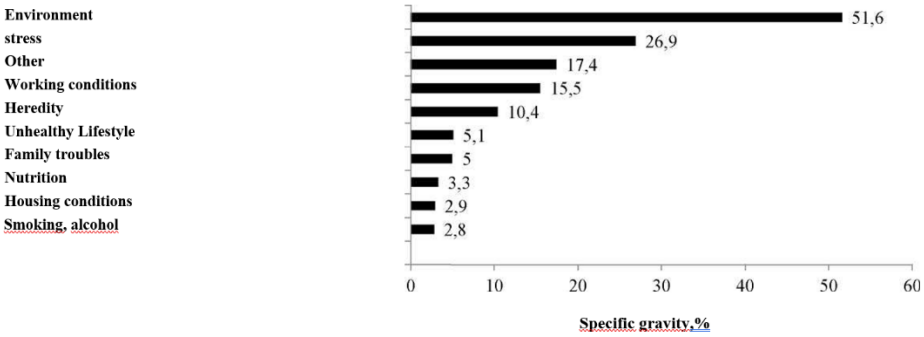

Figure 2. Causes contributing to the occurrence of diseases of the nasal cavity and paranasal sinuses (according to respondents)

The majority (71.2%) of patients prefer to receive medical care in state organizations, 27.2% also use private commercial organizations (PCOs), 1.6% - only PCOs, and the predictors of choice are age, family composition and social status of the patient.

It was found that the half of patients (50.8%) receive the necessary medical care "as a rule", only a quarter (25.2%) - "always", slightly less than a quarter (23.1%) - "periodically" and 0, 9% - "never". The very fact of the lack of perseverance of the respondents in obtaining the necessary medical care testifies to the non-compliance with the standards of diagnostics and treatment when it is provided by medical institutions, which ultimately reduces the quality of medical care.

Estimates of state insurance medical care (SIMC) include: "good" (40.8%), "satisfactory" (41.5%), "bad" (8.0%), "very bad" (1.6%), "they can't say anything about SIMC " 8.1%. The primary factor is the availability of medical care, as well as whether the patient is an outpatient or inpatient, self-reported health and the cause of the disease - external factors, both related to medical care - injuries, operations, dental care, and weather. 82.8% are satisfied with the medical service in their polyclinic or hospital, 4% are partially satisfied, 4.4% are not satisfied (plus 7.4% cannot decide, 1.4% are indifferent). However, it has been found that among inpatients the share of those who are fully satisfied with medical care is slightly higher than among outpatients (88.0% versus 77.5%), partially satisfied is also higher (8% versus 0%), which the total is 96% of hospital patients and 77.5% of outpatients. There are no dissatisfied medical services in the hospital, and in polyclinics they make up 8.8%. Among polyclinic patients, 77.5% are completely satisfied with medical care.

Patients rate the highest level of professionalism, courtesy and attention of the staff in providing medical care in medical institutions. Three characteristics have been identified that make outpatient and hospital care different: professionalism (in favor of the hospital), courtesy and attention of the staff (in favor of the hospital), good conditions (service) (in favor of polyclinics).

The greatest risks of negative assessment by patients - respondents interviewed in the polyclinic of the city and in the hospital, polyclinic relative to the hospital (the ratio of a negative assessment of the polyclinic relative to the hospital) were identified according to the following characteristics: 1) the cost of medical care, 2) the attitude of staff to patients (politeness, attention, etc.), 3) high professional level of staff.

In the city polyclinic, the most significant shortcomings are queues, worn-out equipment and inattentive attitude. The greatest differences (27.1%) between polyclinic and hospital patients were revealed on the issue of "unsatisfactory treatment conditions in the city polyclinic", the smallest (9.3%) - "queues". Hospital patients more often note the poor quality of the medical services provided, high cost, lack of trust, self-medicate more often, do not have time for treatment in medical organizations, but less often indicate queues, although these reasons are related, and the severity of movement to a medical institution.

4. Discussion

The analysis of the incidence of nasal cavity and paranasal sinuses pathology allows us to conclude that this category of patients prevails among all hospitalized ENT morbidity[10]. Outpatient also make up a significant percentage of all otorhinolaryngological patients (28.0%), although they are inferior to the number of patients with pharynx diseases (38.8%)[11,12]. A significant relationship was found between the appeal for otorhinolaryngological care and medical and social characteristics: age, gender, family composition, social status, the presence of chronic diseases, self-assessment of health, treatment in an outpatient clinic or hospital [13].

The medical and social characteristics of patients with diseases of the nasal cavity and paranasal sinuses, identified in the course of the study, form the basis of the developed methodological recommendations for improving medical care for this group of patients[14,15].

A sociological study conducted among patients with permanent nose and paranasal sinuses revealed the occurrence of cases in the process of delivery and medical care organization in a hospital (lack of service, poor equipment and lack of medical facilities), in a city clinic (queue, worn-out equipment), inattentive attitude of staff) and the development of recommendations for improving the quality of the medical organization of otorhinolaryngological care, ways to solve the state of observation, consumption of therapeutic and preventive diseases of the cardiovascular system, medicinal diseases of patients with nose and paranasal sinusespathologies[16].

5. Conclusions

The study of the structure of hospital morbidity of ENT organs (according to statistical data) in the ENT department of the City Clinical Hospital No. 4 of Moscow showed that a large nosological group had nasal cavity and paranasal sinuses diseases throughout the entire study period - more than 50, 0%. In second place is ear pathology - about 25.0%, in third place - diseases of the pharynx - about 10.0%.

Author Contributions: Conceptualization, A.C., P.M.; methodology, A.C., P.M., validation, A.C.

Conflicts of Interest: The authors declare no conflict of interest.

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Review Article

International experience and recommendations on audiological screening of schoolchildren: review.

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Abstract: Permanent childhood hearing loss is crucial for speech development and restricts learning abilities. Universal newborn hearing screening programs are well established to detect congenital hearing loss and address the need of hearing-impaired babies. Progressive or acquired permanent hearing loss can manifest later due to genetic causes, intrauterine or postnatal infections, middle ear diseases and excessive exposure to noise when listening the personal audio devices. The hearing loss prevalence in the population of 9 year-olds three times higher compared with newborns. School hearing screening is a part of hearing across the lifespan conception. The article presents international experience and recommendations for the organization of school hearing screening programs. A school-entry hearing test is mandatory, other grades might be screened also. The basic method is pure tone audiometry at frequencies of 500, 1 000, 2 000, 4 000 Hz at 20 dB. Otoscopy and tympanometry can be performed also, while whisper voice speech test is of low sensitivity. The main hearing screening issue is low follow-up of referrals to ascertain audiological assessment. Modern approaches to the prevention of hearing loss in schoolchildren and management of hearing impairements are described. Planning of hearing screening programs requires sufficient human and logistical resources, monitoring of results and quality improvement, all stakeholders engagement.

Keywords: hearing impairment, hearing loss, school hearing screening, screening protocol, pure tone audiometry, guidelines, international experience.

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1. Introduction

Universal audiological screening of newborns makes it possible to detect congenital hearing loss and compensate for impaired auditory function in the first months of a child's life. However, progressive or acquired hearing disorders may develop at a later age. In the absence of complaints of pain and discomfort in the ears, hearing impairment, as well as the attention of parents, doctors and teachers, hearing disorders often remain unrecognized. Children do not receive the necessary treatment to prevent persistent hearing impairment or rehabilitation measures in the case of already formed persistent hearing loss. Hearing impairment hinders speech development and learning, is an obstacle to the assimilation of material in the classroom and academic performance, as well as to full communication and socialization. Accessible education, including for people with disabilities, is one of the Sustainable Development Goals declared by the United Nations. According to global estimates of the World Health Organization, 34 million children in the world have socially significant hearing impairments, while about 60% of cases of hearing loss are preventable [1]. The prevalence of persistent hearing impairment among 9-year-old children increases almost threefold compared to congenital forms [2]. Therefore, screening of hearing disorders in school-age children is included in the concept of detecting hearing loss throughout life2 [3].

2. Etiology of hearing disorders in school-age children

The causes of hearing impairment can be classified depending on the level of localization of the pathological condition. Conductive hearing loss occurs when sound conduction is disrupted by mechanical obturation of the external auditory canal by sulfur plugs, foreign bodies or Sensorineural hearing loss, detected at preschool and school age in the absence of a well-established acquired cause, is most likely due to pathological mutations in genes, encoding the synthesis of structural proteins of the inner ear, while hearing impairment may be congenital or manifest in the postnatal period. Among children with confirmed hereditary sensorineural hearing loss, from 13 to 26% were not detected by the audiological screening program of newborns [4, 5]. A systematic review of studies on combined audiological and genetic screening showed that genetic mutations are detected in 1.4% of newborns with a negative result of audiological screening [6]. The late onset is characteristic of half of the cases of hearing loss caused by intrauterine cytomegalovirus infection [7]. Acquired sensorineural hearing loss can occur due to infectious diseases (measles, mumps, rubella, flu), the use of ototoxic drugs (aminoglycosides, platinum preparations), traumatic brain injuries. In rare cases, the cause of hearing impairment is neurodegenerative diseases involving the auditory nerves and central auditory pathways (neurofibromatosis). These diseases are classified as risk factors for hearing loss with the requirement of referral for an audiological examination [8]. Recently, special importance has been attached to the risk of irreversible damage to the auditory receptors with excessive noise exposure associated with prolonged listening by schoolchildren to personal audio devices [9].

3. Recommendations for conducting audiological screening of schoolchildren

The first study to evaluate the medical technology of audiological screening of schoolchildren is considered to be a 2007 review by J. Bamford et al. At that time, about 90% of schools in England, Scotland and Wales provided hearing testing for children before entering school, however, there was an insufficient amount of evidence-based research on this issue, as well as the need for uniform national recommendations [10]. The results of this review were used to form recommendations for audiological screening in childhood by the American Academy of Audiologists pathological secretions. Violation of sound conduction in the middle ear can be caused by inflammatory purulent or non-purulent processes in the tympanic cavity (acute and chronic purulent otitis media, exudative otitis media, adhesive otitis media), acute inflammation or persistent dysfunction of the auditory tube, perforation of the eardrum, post-traumatic or congenital pathology of the auditory ossicles. In 2011, at the Congress of the European Federation of Audiological Societies, the European Consensus on hearing screening of preschool and school-age children was approved [11]. In order to implement school screening programs for the early detection, treatment and rehabilitation of children with hearing impairments, it is necessary to raise awareness of the authorities and society, exchange knowledge and experience between countries, use information technologies and telemedicine capabilities in the provision of sign language assistance. The experience of Polish audiologists using the developed platform for the examination of sensory functions in children is presented [12]. In 2021, the program for the prevention of hearing loss and deafness of the World Organization The results of existing practices in the field of audiological screening in different age groups, including among schoolchildren, were systematized.4 When forming the program protocol, it is necessary to clearly define the main screening parameters: the target population (all students, high-risk children, age groups); target condition (degree of hearing impairment, one- or two-sided), conditions (at school, in a medical organization). Taking into account the large scale of the target population, a preliminary assessment of the costs of implementing screening and its economic efficiency is necessary [13]. In accordance with this, a method of screening hearing testing (one or a combination of methods) is chosen, criteria for a positive screening result are established, in which a referral to confirming diagnostics. Also, when implementing a screening program, quality criteria are determined that are necessary for monitoring the results and making changes to the protocol to measure effectiveness (coverage of the target population, the proportion of children identified by screening, the proportion of children who have passed a confirmatory diagnosis). The degree of hearing impairment. It is recommended to identify hearing thresholds at the level of 20 dB, since even a slight degree of hearing impairment limits the ability to learn. However, in the absence of a soundproof room with background noise above 40 dB, the number of positive screening results increases, including false positives, which increases the workload of specialists at the stage of confirmatory diagnosis. Age and frequency of the event. A hearing test is considered mandatory before entering school. In countries where kindergarten is a stage of school education, hearing testing of children aged 3-7 years also refers to audiological screening of schoolchildren. If possible, it is recommended to conduct a hearing test in the learning process (for example, in grades 1, 3, 5, 7 and 9). The venue. To ensure full coverage of audiological screening, the place of its conduct should be as close as possible to the students, i.e. the organization of screening in the conditions of school. It is also possible to conduct screening in medical organizations when organizing comprehensive medical examinations or visits for the purpose of vaccination. Staff.

Teachers, secondary medical staff of schools, and other personnel who have received appropriate training can participate in conducting audiological screening of schoolchildren. Repeated screening and diagnostic examination are carried out by specialists of surdologists, audiologists, otorhinolaryngologists. Diagnostic significance it is an objective indicator of the effectiveness of an individual method or the entire screening program. Depending on the combination of screening data and confirmatory diagnostics, the final results are divided into true positive (TP – true positive), false positive (FP – false positive), false negative (FN – false negative) and true negative (TN – true negative). Based on the ratio of the results, the main indicators of the diagnostic value of the method are calculated:

■ sensitivity – the probability of a positive screening result in a child with hearing impairment TP/(TP + FN) x 100%;

■ specificity – the probability of receiving a negative screening result in a child without hearing pathology TN/(TN + FP) x 100%.

The criteria for a positive/negative screening result should be chosen in such a way as to ensure the greatest sensitivity and specificity both in relation to a particular method and the audiological screening program as a whole. To increase the diagnostic significance, screening may include several stages with repeated immediate or delayed testing of children with a positive result [14].

4. Research methods

Tonal audiometry is used as the main method for audiological screening of schoolchildren, including preschoolers starting from the age of 3. It is mandatory to conduct a test at frequencies of 500, 1,000, 2,000 Hz, while the range of the studied frequencies can be 250-8000 Hz. In high school, it is desirable to be examined at high frequencies, taking into account the increased risk of exposure to excessive noise and personal audio devices. The intensity of a test stimulus of 20 dB with a single or multiple presentation is recommended for screening. When conducting a study in the absence of noise insulation at a frequency of 500 Hz, the intensity can be set to a higher level. The study can be carried out using stimuli of several intensities, starting from a higher level, which helps to increase the specificity of the test and reduce the number of children in need of confirmatory diagnosis, but increases the duration of testing. It is possible to use the method of recording otoacoustic emission in children under 3 years of age or at the level of mental development corresponding to the age of three. Otoscopy and tympanometry can be performed for children with a positive result of screening tonal audiometry in the presence of equipment and specially trained personnel or with the participation of a specialist doctor to exclude pathology of the outer and middle ear. Criteria A positive screening for tympanometry is a tympanogram of type B and type C (in which different levels of intrathympanic pressure can be taken into account as critical – from -150 to -200 daPa). Tympanometry is recommended for children of preschool and primary school age, taking into account the high prevalence of exudative otitis media in this age group. To screen the hearing of children over 9 years old, a test of speech intelligibility in noise (digit triplet test) can be used. It is a fairly effective alternative to tonal audiometry in countries with limited health resources or in remote areas, since applications specially designed for smartphones (for example, hearWHO) can be used for its implementation [15, 16]. It is not recommended as a screening method to study the hearing of schoolchildren with whispered speech due to low sensitivity.

5. The world experience of audiological screening of schoolchildren

Despite the existing recommendations, audiological screening of schoolchildren is not a widespread practice. According to the EUSCREEN project implemented in 2018-2020, during which existing audiological screening programs were studied in 47 countries, universal (mass) audiological screening of schoolchildren is being implemented in 17 countries, screening is carried out selectively or irregularly in 8 more countries [17]. The intensity used as a criterion for passing tonal audiometry is in the range of 20-40 dB, in most cases – 30 dB in children 3-4 years old and 25 dB in children over 4 years old. In most programs, testing is carried out at frequencies of 500– 4000 Hz. Screening coverage is 92-99%, the proportion of children identified by screening is 7.6–7.9%, the proportion of children who have undergone confirmatory diagnostics, – 58-77%. A systematic review of 65 studies on audiological screening of schoolchildren, published by M. Yong et al. in 2020, it also indicates an insufficiently wide implementation of screening programs, a variety of protocols and criteria [18]. In the USA, screening is implemented in 66% of states. Pilot programs have

been implemented in other countries, according to the results of which widespread implementation is recommended, but there is no information about its results. Most studies are based on conducting tonal audiometry in school conditions, the criterion of direction is the absence of a response at one frequency (most often 500, 1 000, 2 000, 4 000 Hz, with a range of 500-8000 Hz) at an intensity of 20 dB. As additional research methods otoscopy, tympanometry, registration of otoacoustic emission are used. The proportion of children identified with suspected hearing impairment varies from 0.16 to 15%. As in the EUSCREEN project, the problem of continuity of screening is noted: the proportion of children with known results of a complete audiological examination is 10-65%. In the Republic of Yemen, where universal audiological screening of newborns is not carried out, a pilot study of auditory function was conducted among 2,200 primary school students, average age 7.5 years. The protocol of audiological screening included otoscopy, audiometry with tones of 20 dB intensity at frequencies 500, 1 000, 2 000, 4 000 Hz. The criterion of the direction was the absence of a response on at least one frequency from one or two sides. According to the results of screening, 11.6% of children had hearing impairment. Conductive hearing loss of I–II degree was detected in 86% of children, the most common cause was acute and exudative otitis media. Sensorineural hearing loss was diagnosed in 14% of children [19]. Several pilot studies of audiological screening of schoolchildren have been implemented in Russia. A.V. Pashkov et al. automatic audiometry was used in 112 schoolchildren (average age 12 years) with the help of a special hardware and software complex at frequencies 500, 1 000, 2 000, 4 000 Hz, the accuracy of the study was compared with the results of standard tonal threshold audiometry. Hearing disorders were detected in 20 (18%) patients, of which 5 had sensorineural hearing loss [20]. Another Russian study included a sample of 216 children in grades 1-11 [21]. The screening protocol differs from the recommended one and includes otoscopy, tympanometry, registration of otoacoustic emission, examination whispered and spoken speech. As a result, 44% of children did not have otoacoustic emission from one or both sides. According to the results of the extended diagnosis, 13 (6%) children had a hearing impairment of I–II degree. Despite the absence of regular audiological screening programs that comply with international recommendations, medical examinations of schoolchildren have been carried out in Russia for many years. In accordance with the procedure for monitoring minors, an examination by an otorhinolaryngologist in a polyclinic is mandatory for children aged 1, 3, 6, 7, 15, 16, 17 years (Order of the Ministry of Health of the Russian Federation No. 514n dated 10.08.2017). During otoscopy, pathology of the outer and middle ear can be detected, hearing is checked by whispering speech, followed by referral to a surdologist for audiological diagnostics. If appropriate equipment is available, tympanometry can be performed Thus, hearing screening is carried out before entering school and in high school, however, hearing impairment may be missed in elementary and secondary school students, which requires changes to existing regulations.

6. Possibilities of prevention, treatment and rehabilitation of hearing disorders identified as a result of audiological screening of schoolchildren

Prevention of hearing disorders in schoolchildren consists primarily in informing children, parents and teachers about risk factors for hearing loss, the formation of proper ear hygiene skills and safe listening. Vaccination against measles, rubella, mumps, and influenza, which can cause complications in the form of sensorineural hearing loss, plays an important role [22]. Vaccination against pneumococcus has shown high effectiveness in preventing the development of severe hearing loss and deafness due to meningitis [23]. Conductive hearing loss associated with obturation of the external auditory canal by sulfur masses and various foreign bodies is successfully resolved through appropriate manipulations. Hearing impairment due to inflammatory diseases of the middle ear is corrected by drug therapy or surgical interventions. In acute, up to 1 month, pathology of the cochlea receptor apparatus, systemic therapy with glucocorticoids is sufficiently effective, but it is often difficult to establish the period of hearing impairment, especially in the case of unilateral hearing loss [24, 25]. The main means of helping children with sensorineural hearing loss is medical rehabilitation, including hearing replacement for hearing impairment of II–IV degree, including unilateral losses [24, 25]. With mild hearing loss, it is necessary to provide the child with the correct placement in the classroom (the first desks, with a better hearing ear to the teacher), the opportunity to relax from the noise at recess. For any hearing loss, sign language correction is indicated. Cochlear implantation is indicated for children with grade IV sensorineural hearing loss and deafness [24-26]. Cases of severe bilateral hearing loss of this type are usually detected in a timely manner due to the presence of relevant complaints. Audiological screening of schoolchildren is effective in detecting unilateral sensorineural deafness, in which cochlear implantation from extrabudgetary funds can also be recommended.

7. Conclusions

Audiological screening of schoolchildren is the most effective way to timely identify and assist children with hearing impairment. Despite the developed recommendations and conciliatory documents, there are significant differences in protocols, used audiological tests and referral criteria for confirmatory diagnosis and treatment. To increase the reliability and effectiveness of audiological screening programs for schoolchildren, as well as the possibility of comparing screening results in different countries, studying the epidemiology of hearing disorders in this age group, it is necessary to form standardized protocols. On the other hand, the different capabilities of health systems in different countries require more flexible approaches to the development and implementation of audiological screening programs for schoolchildren, taking into account available resources. When forming audiological screening programs for schoolchildren, it is necessary to take into account the following aspects: provision of the surdological and otorhinolaryngological service with appropriate human and material resources for timely and full-fledged assistance to children identified as a result of screening; approval of procedures for referral and observation of children with identified hearing disorders and ear diseases; availability of medical and surgical methods of treatment of ear diseases, technologies for rehabilitation of children with hearing impairment. Audiological screening of students should be part of routine medical examinations, along with a general medical examination, a check of vision, teeth, etc. When planning an audiological screening program for schoolchildren, the responsibility of stakeholders should be determined, issues of data collection and monitoring, quality control and efficiency improvement should be worked out. Like any screening program aimed at identifying various pathological conditions, the hearing test of schoolchildren should not be limited to the use of screening techniques. In the absence of a confirmatory diagnosis, treatment and medical rehabilitation, all screening efforts result in an inefficient expenditure of resources

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Article

Evaluation of the effectiveness of local anesthetics during septoplasty and tonsillectomy.

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Abstract: Surgical trauma provokes body's stress response with activation of inflammatory, endo-crine, metabolic, and immunological factors, which is believed to be necessary and beneficial response. Aim of the study was to compare the effectiveness of local anesthetics lidocaine and articaine in septoplasty and tonsillectomy in terms of assessing the severity of stress reactions. Patients and Methods: 125 patients with nasal septum deviation (NSD) and chronic tonsillitis (CT) were observed. Patients with NSD were divided into 2 groups: 1A – 32 patients treated by 2% lidocaine local infiltration analgesia (LIA); 1B – 30 patients treated by 2% articaine LIA. Corresponding groups of patients with CT were 2A (32 patients) and 2B (31 patients). For all patients, heart rate variability (HRV), high, low and very low frequency components were measured. Results: Estimation of group variances of HRV showed there were some disadaptation in groups 1B and 2A. High dispersion of SDANN, SDNN index and rMSSD in 1B group, SDANN values in 2A group indicate the sympathetic/parasympathetic imbalance. High frequency component were augmented in 2B group which pointed out prevailing parasympathetic tone but its high dispersion was indicative of disadaptation as well. Conclusion: Thus, with the local infiltration application of an articaine solution during septoplasty, the autonomic nervous system dystonia is observed in the early postoperative period. When anesthesia with lidocaine solution during tonsillectomy, there is also a breakdown of adaptive responses against the background of surgical stress. Based on the above data, of the presented local anesthetics, lidocaine is more effective in septoplasty, and articaine in tonsillectomy.

Keywords: septoplasty, tonsillectomy, autonomic nervous system, heart rate variability

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1. Introduction

It is known that any surgical intervention entails a consistent development of stress reactions. Such interventions in otorhinolaryngology do not constitute an exception. Some of the most common are septoplasty and tonsillectomy. For example, in 50 clinics in Germany, they are leaders among surgical interventions. At the same time, between 2007 and 2010, the number of tonsillectomy in Germany almost doubled from 4,659 to 8,799 [1].

Surgical trauma provokes body's stress response with activation of inflammatory, endocrine, metabolic, and immunological factors, which is believed to be necessary and beneficial response [2]. However, an excessive increase in the production of various components of the surgical stress response can lead to hemodynamic instability, metabolic disorders, multiple organ failure, and even death [3-5]. In addition, stress includes changes in behavior, autonomic nervous system function, and increased secretion of certain hormones such as cortisol, corticosterone, and adrenal catecholamines [6]. Higher blood pressure and heart rate during stress reflect the predominance of

sympathetic nervous system activity [7]. Psychological stress decreases the high-frequency component of heart rate variability (HRV) and increases the low-frequency component of HRV [8]. HRV decreases in patients with depression, manifestations of high hostility and anxiety [9]. Stress lowers the body's resistance to negative health effects [10]. The autonomic nervous system facilitates the physiological adaptation of the body in short periods, but this process can be disrupted if the synthesis of mediators such as adrenaline in the adrenal medulla is not stopped even if there is no physiological need for them.

One of the important directions in the prevention of stress-related disorders is the reduction of nociceptive sensitivity with the help of local anesthetics. Recently, local anesthetics such as lidocaine and articaine have been widely used in surgical practice. Lidocaine blocks the voltage of closed fast sodium channels in the cell membrane of postsynaptic neurons, preventing depolarization and inhibiting the formation and propagation of nerve impulses. At lower blood concentrations, lidocaine only affects sensory neurons, while at higher concentrations, its effects become more generalized.

Lidocaine also has anti-inflammatory and immunomodulatory properties. Compared to other agents in its class, lidocaine has a rapid onset of action and an intermediate duration of effect [11]. Some animal models show that lidocaine can interrupt part of the nociceptive pathway [12, 13]. Furthermore, the analgesic effect may be mediated by the effect of lidocaine on N-methyl-D-aspartate receptors. The action of articaine depends on the state of sodium channels: it has the highest affinity for open channels, an average affinity for their inactive state, and the lowest affinity when they are at rest [14]. The onset of anesthesia after the introduction of articaine with a solution of adrenaline in a ratio of 1: 100,000 occurs from 1 to 9 minutes after injection.

The onset of action of 4% articaine with 1:200,000 adrenaline occurs in 1.5–1.8 minutes with maxillary infiltration and in 1.4–3.6 minutes with blockade of the inferior alveolar nerve [15, 16]. The full effect of articaine lasts approximately 1 hour. Both concentrations give a rapid onset and severity of analgesic effect for bone (approximately 1 hour) and soft tissues (3-5 hours) [17]. It is believed that the potential efficacy of 4% articaine with 6 μg / ml of adrenaline is 2.8 times greater than that of lidocaine [18].

However, there are very few works on the comparative evaluation of lidocaine and articaine during septoplasty, and during tonsillectomy, no literature was found in the literature available to us. In this regard, the aim of the study was to compare the effectiveness of local anesthetics lidocaine and articaine in septoplasty and tonsillectomy in terms of assessing the severity of stress reactions.

2. Patients and Methods

The study included 125 people with deviated septum and chronic tonsillitis. Depending on the type of surgical intervention, the patients were divided into 2 groups: group 1 (62 patients) underwent septoplasty, group 2 (63 patients) underwent tonsillectomy. In addition, each group was divided into subgroups in which anesthesia was performed with either 2% lidocaine solution or 2% articaine solution (Table 1). The injected volume of each anesthetic did not exceed 20 ml.

Septoplasty was performed under local application and infiltration anesthesia with 2% lidocaine solution in subgroup 1A and 2% articaine solution in subgroup 1B. After the surgical intervention, the nasal cavity was tamponed on both sides with gauze swabs soaked in antibacterial ointment. Patients with chronic tonsillitis underwent bilateral tonsillectomy under local infiltration anesthesia with 2% lidocaine solution in subgroup 2A and 2% articaine solution in subgroup 2B. In septoplasty after application anesthesia, infiltration anesthesia was started from the anterior sections of the nasal septum, moving deeper, simultaneously hydroseparating the mucous membrane and perichondrium from the cartilage. Next, hydroseparation was monitored throughout the surgical field, including the nasal cavity floor and bone section on both sides. After infiltration anesthesia, an arcuate incision was made in the mucous membrane of the nasal septum in the transitional skin fold area, 1-1.5 cm away from it. The side of the incision usually corresponded to that side of the nasal cavity, where the septum was more curved. The section met the principles of "maximum sufficiency", i.e. be wide enough for cartilage manipulation. Bluntly, with the help of a raspator, the mucous membrane and perichondrium were exfoliated from the quadrangular cartilage. Next, the nasal cavity floor and the bone sections were distinguished, if they had a curvature. After the cartilage and bone sections were completely isolated on one side, they moved to the other side of the nasal septum. In a similar way, after the cut of the quadrangular cartilage, the mucous membrane and perichondrium were exfoliated, up to the bone sections. Using Killian's nasal speculum, the exposed cartilage was positioned between its jaws and the curved portion was removed using scissors or a Bellanger scalpel. It should be noted that all patients of group 1 had deformities of the nasal septum in the form of a bone ridge or spike, which were knocked off with a chisel and

hammer during the operation. Next, the mucoperiosteal membranes were laid along the midline and, using a raspator, an audit was carried out for the remaining curved parts of the cartilage and bone protrusions.

Table 1. Study Design

		1 group		2 group	
		1A subgroup	1B subgroup	2A subgroup	2B subgroup
Quantity, pers.	Men	19	16	20	17
	Women	13	14	12	14
Age, years	Min	17	20	18	17
	Max	45	44	42	46
Local anesthesia		2% lidocaine solution	2% articaine solution	2% lidocaine solution	2% articaine solution

During tonsillectomy after application anesthesia, local infiltration anesthesia of the patient was performed with the indicated anesthetics in a sitting position at 5 points: above the upper pole of the tonsil, at the descent of the palatoglossal and palatopharyngeal arches, in the region of the upper pole of the tonsil, in the region of the middle pole of the tonsil, in the region the lower pole of the tonsil (at the base of the palatoglossal arch, in the projection of the 8th lower tooth), in the region of the palatopharyngeal arch of the tonsil. The needle was inserted to a depth of 1 cm, with each injection 2-3 ml of an anesthetic solution was injected. The operation was started 3-5 minutes after the end of the injections. A scalpel was used to make an incision in the mucous membrane of the anterior palatine arch on the right 0.5-0.7 cm. Then, the palatine tonsil was isolated in a blunt way. After that, the tonsil was taken on a clamp, retracted downwards, and with a sharp raspator was separated from the palatoglossal and palatopharyngeal arches, starting from the upper pole, gradually descending to the middle sections and the lower pole. When separating the tonsil, its tissue was captured with forceps along with the capsule. The tonsil on the clamp was brought down and medially, and cut off at the base with the help of Bohon's loop. At the same time, the loop was pressed against the side wall so that the entire amygdala and its lower section passed through the loop and were cut off in one block. After cutting off the tonsil, a thorough examination of the niches was carried out.

Before surgery, both groups of patients received intramuscular injections of 5 ml of a 0.5% solution of metamizole sodium and 1 ml of a 1% solution of diphenhydramine. 30 minutes before surgery, patients in both groups were placed on a 24-hour ECG Holter monitor MT-200 from Shiller. We studied SDNN (ms) - the standard deviation of all values of R-R intervals for 1 day of monitoring after surgery, as well as its night and day indicators. SDNN corresponds to the full range of all heart rate frequencies.

Normal indicators of SDNN were considered the data presented in the work of D. Nunan et al. (2010), 50±16 ms [19]. Ultra-low heart rate frequency (ULF) were measured by SDANN (ms) - this is the standard deviation of the average R-R intervals calculated over 5-minute intervals. Very low heart rate frequencies (VLF) were studied by the values of the SDNN (ms) index, which characterizes the average values of 5-minute standard deviations of R-R intervals calculated over 24 hours. In addition, we also considered the values of the high- heart rate frequency component (HF), which corresponds to the values of rMSSD (ms) - the square root of the sum of the differences in a consecutive series of R-R intervals [20, 21]. A decrease in ULF and VLF indicates the relative predominance of the action of the sympathetic nervous system, and a decrease in HF indicates a decrease in the action of the parasympathetic part of the autonomic nervous system [22,23]. The obtained values of SDNN, SDANN, SDNN index and rMSSD were compared with the reference values in accordance with the age of each patient (Table 2).

Table 2. Reference values of SDNN, SDANN, SDNN index and rMSSD

Age, years	SDNN (ms)	SDANN (ms)	SDNN Index (ms)	rMSSD (ms)

10–19	176 ± 38	159 ± 35	81 ± 20	53 ± 17
20–29	153 ± 44	137 ± 43	72 ± 22	43 ± 19
30–39	143 ± 32	130 ± 33	64 ± 15	35 ± 11a
40–49	132 ± 30	116 ± 31	60 ± 13	31 ± 11

We used the STATISTICA10.0 program for statistical processing of the results. All data are presented as means and standard deviations. The normality of data distribution in each group was assessed using the Shapiro-Wilk test. To compare normally distributed signs, an unpaired Student's t-test was used, with the distribution of at least one sign that differed from the normal one - the Mann-Whitney U-test.

3. Results

When comparing the standard deviation of R-R intervals between subgroups 1A and 1B was higher in subgroup 1A ($p<0.05$). At the same time, in patients who underwent infiltration anesthesia with articaine, a large dispersion of this indicator was observed, compared with the 1A subgroup ($p<0.05$). In the second group, there were no significant differences between both subgroups in terms of SDNN ($p<0.05$). Comparing the data of both groups, we also did not find any differences in all heart rate rates ($p<0.05$) (Fig. 1, Table 3).

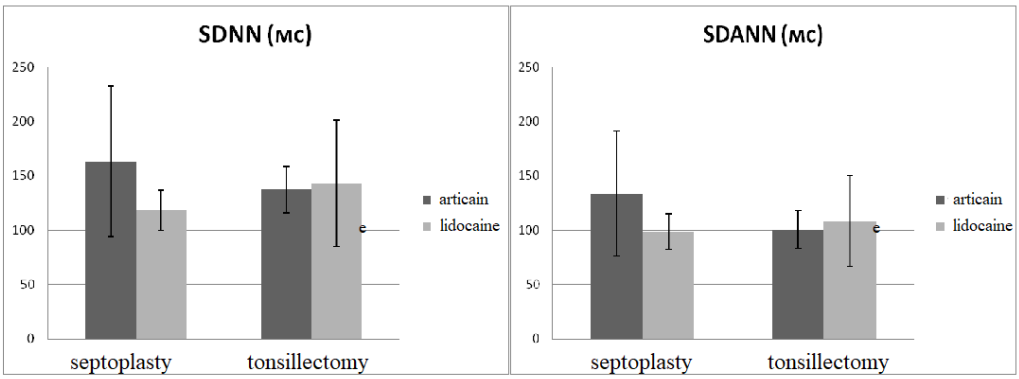

Figure 1. Standard deviation of R-R intervals and SDANN in patients undergoing septoplasty and tonsillectomy.

Table 3. Changes in heart rate variability in septoplasty and tonsillectomy. Note: * - there are significant manifestations between subgroups within the group ($p<0.05$).

subgroup	SDNN (ms)	SDANN (ms)	SDNN Index (ms)	rMSSD (ms)
1A	118±18	98±16	59±9	48±11
1B	163±49*	134±57*	89±46*	63±18*
2A	143±38	108±42	79±39	62±16
2B	137±22	100±18	87±34	49±12*

When using lidocaine in patients of group 1, SDANN was below normal values in 28.5%, in 71.5% - within the normal range. When using articaine, 37.5% of patients after septoplasty had SDANN below normal values, in the same number of patients within the age norm, and in 25% above reference values. In subgroup 2A, 45% of patients had SDANN low, 36% normal, and 18% high ($p<0.05$) (Fig. 1). A large scatter in the data of this indicator in subgroups 1B and 2A was revealed.

In subgroup 1A, all patients had SDNN index values within the normal range ($p<0.05$). When using articaine during septoplasty, it was noted that the dispersion of the SDNN index was high, in half of the patients the index values were normal, and in half they were increased ($p<0.05$). In subgroup 2A, in 72.3% of patients, the SDNN index did not go beyond the reference values, and in 36.4% it was higher than the latter ($p<0.05$). Patients who underwent tonsillectomy under local anesthesia with articaine solution did not significantly differ in SDNN index from those who used lidocaine ($p<0.05$). In group 2, a high dispersion of the SDNN index ($p<0.05$) was observed (Fig. 2).

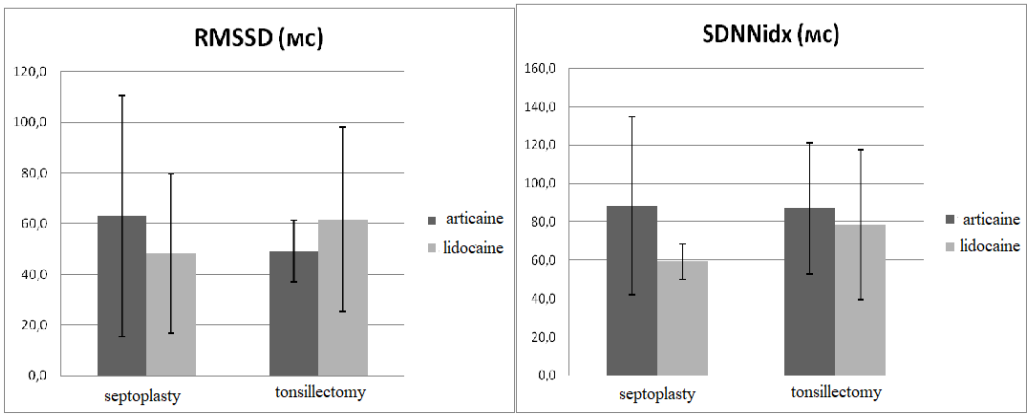

Figure 2. Comparison of SDNN index and rMSSD in patients undergoing septoplasty and tonsillectomy.

In 28.6% of patients of subgroup 1A, rMSSD was significantly higher than the age norm, and in 71.4% it was within the normal range ($p<0.05$). In subgroup 1B, rMSSD was elevated in 50%, unchanged in 25%, and below normal in 25% ($p<0.05$). In all patients of subgroup 2B, rMSSD values did not go beyond the reference values. At the same time, subgroup 2A had a high dispersion of this indicator. Thus, in 18% it was low, in 36.5% it was normal, and in 45.5% it was high ($p<0.05$) (Fig. 2).

4. Discussion

The dispersion of all heart rate frequencies showed that the disruption of adaptive responses was observed in subgroups 1B and 2A. This is evidenced by a large spread of SDANN, SDNN index and rMSSD values in subgroup 1B. This reflects the imbalance of the autonomic and sympathetic parts of the autonomic nervous system in patients of the 1B subgroup. A decrease in SDANN in patients who underwent tonsillectomy with the use of articaine solution may indicate the predominance of the sympathetic component of the ANS, however, they showed a large scatter in its values. In addition, we can not judge the obvious sympathicotonia in this subgroup and the analysis of the VLF. In contrast to ULF, the SDNN index values in most patients of the 2A subgroup were within the normal range.

The high-frequency component of the heart rate in subgroup 2B was increased in the majority, which indicates the predominance of the parasympathetic division of the autonomic nervous system, but its high variability indicates a breakdown in adaptive reactions. In our opinion, the described phenomena during septoplasty occur, most likely, due to the shorter half-life (20 min.), compared with lidocaine (90 min) [24]. In other words, during long-term septoplasty, it is necessary to use lidocaine, despite its lower anesthetic effect and greater toxicity [25-28], due to the ability to maintain its concentration in blood plasma for a longer time. In the second group, the analgesic effect of articaine was more pronounced than in the first group, due to less time spent on surgical intervention.

5. Conclusions

Thus, with the local infiltration application of an articaine solution during septoplasty, the autonomic nervous system dystonia is observed in the early postoperative period. When anesthesia with lidocaine solution during tonsillectomy, there is also a breakdown of adaptive responses against the background of surgical stress. Based on the above data, of the presented local anesthetics, lidocaine is more effective in septoplasty, and articaine in tonsillectomy.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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Article

Coexposure of heavy metals and piracetam destroys adaptive behaviour

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Abstract: In experiments on rats, it was found that lead, cadmium and cobalt salts inhibit the acquisition of an avoidance responses. Cases of increased neurotoxic effect of heavy metals on learning and memory in rats with their combined administration with piracetam have been noted. Ascorbic acid counteracts this neurotoxic impact of the heavy metals and piracetam cooexposure on the adaptive behaviour.

Keywords: heavy metals, piracetam, ascorbic acid, learning, memory.

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1. Introduction

The modern ecological situation is characterized by an oversaturation of pollutants of different nature, the most common and dangerous, among which are supertoxicants – heavy metals [1-2]. The unfavorable environmental situation that has been observed recently in industrially developed regions, according to many researchers, is the reason for the growth of neuropsychic disorders and various cognitive disorders [3]. Neurodegenerative disorders, including Alzheimer's and Parkinson's diseases, have been identified in people engaged in the production of heavy metals [4, 5].

Exposure to heavy metals causes delays in neuropsychic development in children living in industrial cities: memory, learning, motor skills, speech, decreased IQ, etc. [6]. Recently, the toxic effect of heavy metals on the immune system has also been shown [7]. This prompted us to investigate the possibility of correcting such a negative effect of heavy metals with the help of the immunomodulatory drug taktivin [8].

The discussed problem of environmental pollution by heavy metal salts is very relevant for the North Caucasian region, in particular, for North Ossetia, where the amount of heave metals in air, water and soil, due to the developed metallurgical industry, is ten times higher than average.

For the treatment of cognitive disorders, nootropic agents are used, in particular, piracetam, the main property of which is the ability to resist various learning and memory disorders, as shown in numerous animal experiments (9-11).

Until recently, the study of the effect of nootropics and heavy metals on cognitive and mnestic processes was carried out independently, although there is reason to believe that there is a certain interdependence between the effects of the factors under consideration. In particular, the effects of nootropic agents may vary in the presence of heavy metals. It has been shown that the presence of heavy metal salts in drinking water as a solvent, even in minimal concentrations, can significantly affect the effectiveness of the drug [12, 13].

Heavy metals initiate lipid peroxidation by changing the activity of membrane enzymes, while the cells of the central nervous system are most vulnerable to free radical processes [14]. The mechanism of LPO in the cells of the central nervous system is similar to the mechanisms in other tissues, but the intensity of the process is much higher here. In addition, the brain is characterized by a low content of the main components of antioxidant protection. In general, it is the deficiency of the antioxidant system in brain tissue that explains its particular sensitivity to the production of free radical compounds [15].

The main active element of the protective system against the damaging effects of free radicals are antioxidant compounds. The antioxidant properties of ascorbic acid, which is part of the redox

system, are the most important element in the mechanisms of the body's resistance to the effects of toxic substances, including the harmful effects of heavy metals [16].

In this scientific work, we investigated the features of the formation of adaptive reactions of rats under the combined effect of various heavy metal compounds, the reference nootropic drug piracetam and ascorbic acid.

2. Materials and methods

The study was carried out on mongrel white male rats weighing 200-250 g, which were kept under normal light conditions and free access to water and food. The following substances were injected intraperitoneally into the animals: reference crystal piracetam (AKRIKHIN, Russia; 300 mg/kg), lead diacetate (0.08 mg/ml), cobalt sulfate (0.08 mg/ml) or cadmium chloride (0.08 mg/ml), ascorbic acid (VIFITECH, Russia; 250 mg/kg).

The development of the conditioned reflex of active avoidance (CRAA) was carried out in a shuttle box divided by a partition with an opening for two identical compartments measuring 19x21x22, with an electrified grating floor. The rat was placed in the box 5 minutes before the start of the experiment. The CRAA production began by determining the threshold of individual sensitivity of a particular animal to electricity. The sensitivity threshold was considered to be the one that caused the animal to move around the box. 10 seconds after the isolated action, an unconditioned stimulus was added to the conditioned stimulus (700 Hz sound) – electricity flow of 0.5-0.6 mA. When the animal passed into the other half of the box through the opening (the escape response), the sound and electricity were turned off. If the animal moved to the other compartment away from the sound signal (the avoidance response), then there was no electricity, and the sound stopped. If the animal did not relocate under the influence of the stimuli, then 10 seconds later the stimuli were turned off automatically. Each experiment consisted of 25 attacks with a 30-second inter-signal period. The experiments were carried out during the period of 5 days until the acquisition of a stable reflex, which was estimated according to the training criterion (no less than 80% of avoidance reactions out of the number of attacks). The number of avoidance reactions, escape reactions and inter-signal reactions (ISR) was recorded.

Two series of experiments were conducted. In the first series, 4 hours before the development of the avoidance reaction in each of the 5 experimental days, rats were intraperitoneally injected with a salt solution of one of the heavy metals, and a solution of piracetam was administered half an hour later. Control animals were injected with an equivalent volume of solvent half an hour before the experiment. In the II series, in addition to these substances, a solution of ascorbic acid was injected either before the introduction of a solution of a heavy metal salt (lead diacetate, cadmium chloride), or after (experiments with cobalt sulfate). Statistical processing of the studies was carried out using parametric (Student's t-test) and nonparametric (Wilcoxon and Mann-Whitney criteria) methods. The differences were considered significant at $p<0.05$. Calculations were performed using Microsoft Excel computer programs; Origin Pro 6.1 and Statistica for Windows 7.0.

3. Results

The presented experimental data of the I series (Fig. 1) show that the average values of avoidance in animals treated with piracetam were comparable with the control ones. Heavy metals inhibited animal learning. The greatest oppression was exerted by cadmium and cobalt salts. Against the background of heavy metals, there was no statistically significant increase in the number of avoidance reactions from experiment to experiment in general, which indicates a deep inhibition of learning; animals avoided exposure to current only in 10-17% of all possible cases of its exposure.

The effect of piracetam with the combined substances exposure was expressed only in a decrease in the inhibition of learning by pre-administered heavy metals. The effect of cobalt sulfate was reduced by piracetam in the last three experimental days, and the number of avoidance reactions when introducing the metal with piracetam was greater than without the drug. At the same time, however, the level of avoidance remained below the control; the latter indicates that the oppression of learning manifested also in these conditions. It should also be noted that cobalt sulfate reduced the activity of piracetam, so that the number of avoidance reactions with joint administration was less than with separate administration of nootropics.

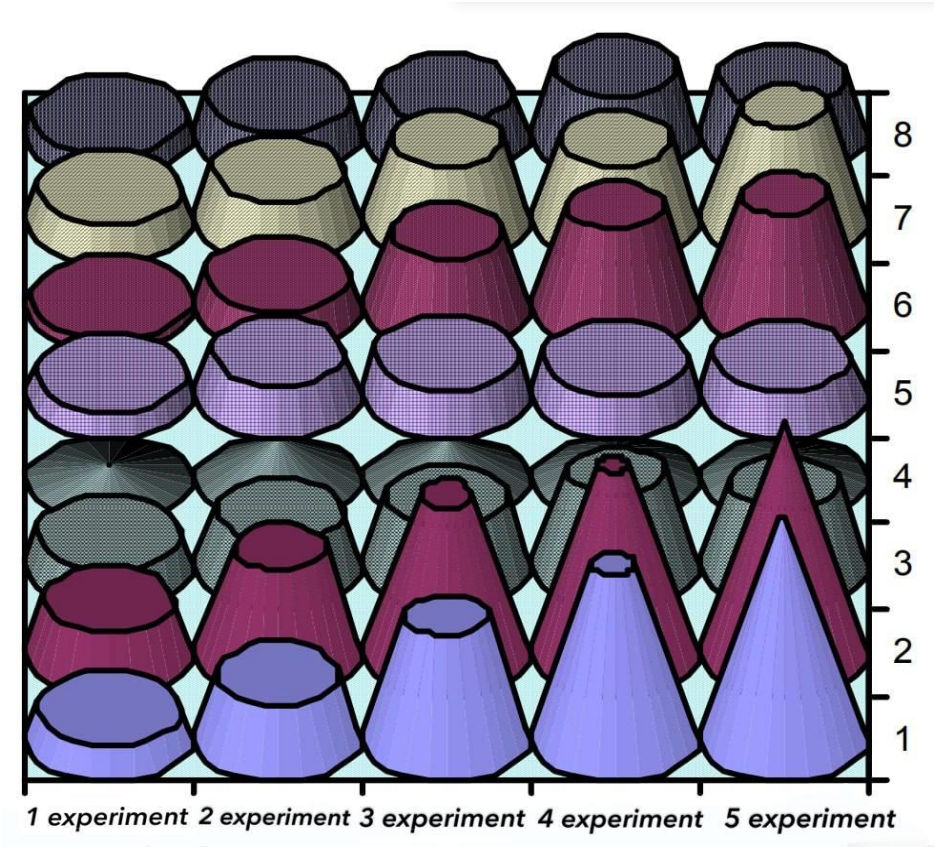

Figure 1. Acquisition of the conditioned reaction of active avoidance in the first series of experiments: on the abscissa axis – the number of experiments; on the ordinate axis – the number of avoidance reactions (% relative to all presentations) against the background of: 1 – saline solution; 2 – piracetam; 3 – lead diacetate; 4 – cobalt sulfate; 5 – cadmium chloride; 6 – piracetam and lead diacetate, 7 – piracetam and sulfate cobalt, 8– piracetam and cadmium chloride.

Of the three days in which learning was inhibited by lead diacetate, piracetam reduced the inhibition only on the last day, in which the level of avoidance with combined exposure to metal and nootropic was higher than with separate administration of metal; however, avoidance remained below the control. In addition, on this day, as on the others, lead diacetate, in turn, reduced the activity of piracetam, and the number of avoidance reactions when nootropic drug was administered against a metal background was less than when it was administered separately. Moreover, the combined administration of piracetam and lead salt led to additional inhibition – a decrease in the number of avoidance reactions relative to the control in the first two days, in which it was absent with separate metal exposure, so that the level of avoidance became lower than the control for all 5 experimental days.

The number of avoidance reactions with the combined administration of cadmium chloride and piracetam was greater than with the separate administration of metal salt, remaining, however, 2.5 times less than the control value. At the same time, the effect of piracetam was weakened by the preliminary injection of cadmium chloride.

The obtained experimental results indicate that along with the positive effect of piracetam, expressed in a decrease in the depressing effect on learning and memory of rats from heavy metal salts, a significant number of cases have been noted in which the nootropic effect was weakened by the preliminary injection of metals.

In the II series of experiments, it was shown that piracetam accelerates the formation of CRAA on all experimental days (Fig. 2, 3, 4), which is different from the effect of the drug in the 1st series. This ambiguous effect of nootropics on learning and memory was noted earlier by other researchers [17], which indicates the sufficient prevalence and significance of this fact. The ambiguity of the piracetam effect can be explained by the influence of several factors, among which we note the following:

- features of the crystal structure of piracetam, namely, the existence of several polymorphic forms of the drug with different physico-chemical properties and, as a consequence, with different pharmacological activity [18];

- environmental factor (interaction of the drug with xenobiotics that have a negative impact on the functioning of biological systems, in particular, on the central nervous system);
- the chemical composition of the water used for solutions, in particular, the presence of certain amounts of heavy metal compounds in it.

This can be confirmed by the results of a UV spectrometric study of the kinetics of dissolution of crystalline piracetam in aqueous solutions of heavy metal salts at concentrations of lead diacetate, cadmium chloride and cobalt sulfite equal to and below the established MPC for drinking water [12, 13, 19]. The revealed features of the absorption spectra of piracetam solution in the presence of these active salts of heavy metals allowed us to conclude about their catalytic effect on the structure of the drug, which, in turn, is the cause of the unstable nootropic effect of piracetam.

The experiments carried out showed a deterioration in the acquisition of conditioned reflex in the shuttle chamber in rats against the background of the combined effect of piracetam and lead diacetate (Fig. 2). It should be emphasized that the level of CRAA in rats receiving injections of piracetam and lead diacetate was less than the indicators of rat teaching with separate exposure to metal, which is consistent with the data of experiments I series. Consequently, with the combined action of these substances, there is a stronger inhibition of learning and memory.

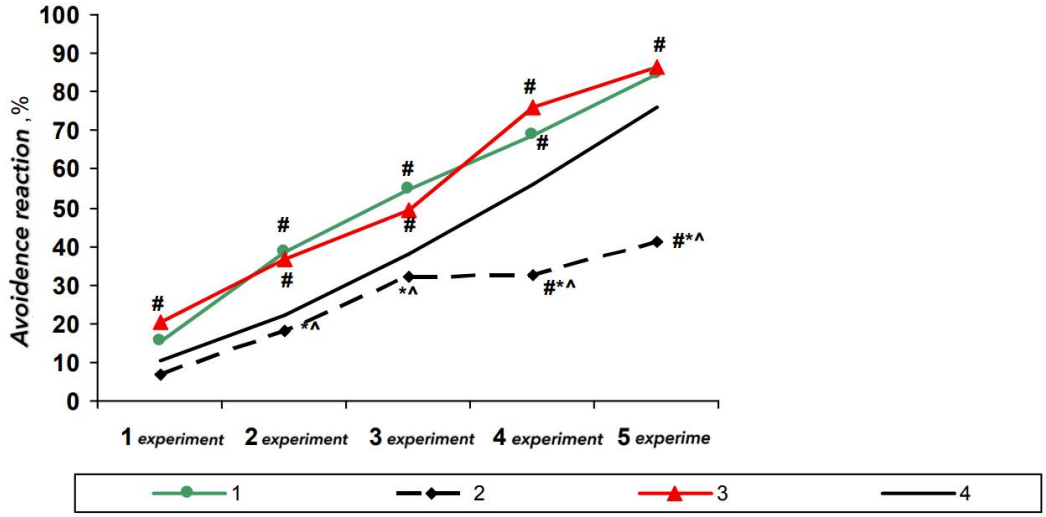

Figure 2. Acquisition of the conditioned reaction of active avoidance under the influence of ascorbic acid, piracetam and lead diacetate:
on the abscissa axis – the number of experiments; on the ordinate axis – the number of avoidance reactions, % relative to all presentations. 1 – piracetam; 2 – piracetam + lead salt; 3 – ascorbic acid+ piracetam + lead salt; 4 – control.
– $p<0.05$ relative to the control; * – $p<0.05$ relative to the experimental group of animals that were injected with piracetam solution; ^ – $p<0.05$ relative to the experimental group of animals that a solution of ascorbic acid was injected, followed by a solution of piracetam and lead diacetate.

Ascorbic acid eliminated the suppression of avoidance under the influence of heavy metals. From the first experiment, the learning indicators in animals with the combined administration of lead diacetate, piracetam and ascorbic acid were higher than the control and statistically significantly exceeded the indicators of rats that did not receive a vitamin solution (Fig. 2).

When CRAA was formed against the background of the combined action of cadmium chloride and piracetam, as in series I, there was a significant decrease in indicators relative to the control and the group receiving piracetam injection. Cadmium weakened the effect of nootropics. As follows from the presented data (Fig. 3), previtamination of animals significantly facilitated the CRAA acquisition in rats injected with a solution of piracetam and cadmium salts. From the first experiment, the percentage of avoidance reactions against the background of the combined action of cadmium chloride, piracetam and ascorbic acid was greater than in the group of animals that were injected with a metal salt solution and a nootrope.

Cobalt sulfate, as well as the compounds of other heavy metals studied by us, had a negative impact on the CRAA acquisition in both series of experiments conducted by us (Fig. 1, 4). Moreover, when a nootropic drug was administered against the background of cobalt salts, as well as in experiments with lead and cadmium compounds, there was a greater inhibition of the avoidance reaction than with a separate introduction of metal.

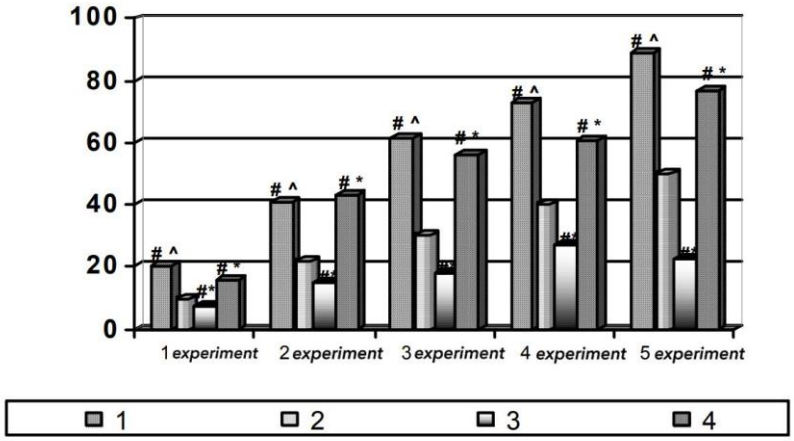

Figure 3. Acquisition of the conditioned active avoidance reaction against the background of the combined action of ascorbic acid, piracetam and cadmium chloride:
on the abscissa axis – the number of experiments; on the ordinate axis – the number of avoidance reactions, % relative to all presentations 1 – piracetam; 2 – control; 3 – piracetam + cadmium chloride;4 – ascorbic acid + piracetam + cadmium chloride.
- p<0.05 relative to the control (physical solution); * – p<0.05 relative to the experimental group of animals injected with piracetam; ^ – p<0.05 relative to the experimental group of animals injected with cadmium chloride and piracetam.

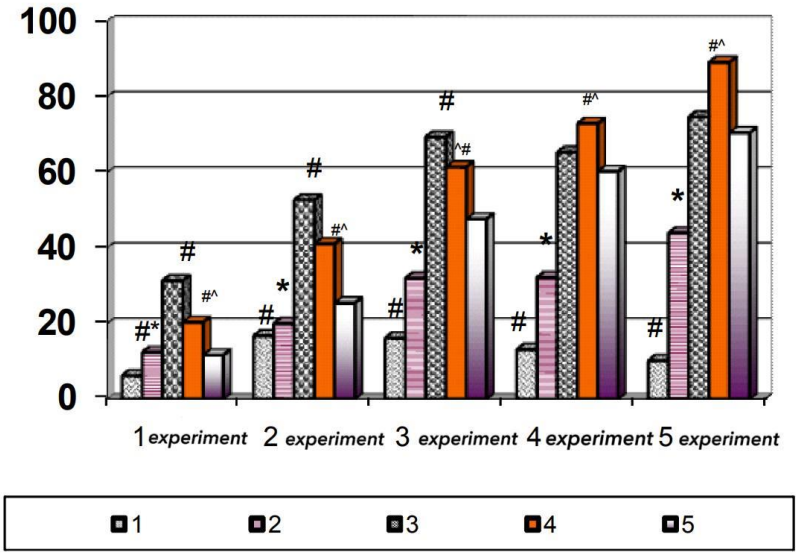

Figure 4. Acquisition of the conditioned active avoidance reaction against the background of the combined action of piracetam, cobalt sulfate and ascorbic acid:
on the abscissa axis – the number of experiments; on the ordinate axis – the number of avoidance reactions, % relative to all presentations 1 – cobalt sulfate; 2 – cobalt sulfate + piracetam; 3 –cobalt sulfate + piracetam + ascorbic acid; 4 – piracetam; 5 – control.
– p ‹ 0.05 relative to control; * – p ‹ 0.05 relative to the experimental group of animals injected with piracetam solution; ^ – p ‹ 0.05 relative to the experimental group of animals that were injected with a solution of cobalt sulfate and piracetam.

The administration of the antioxidant significantly increased the learning rate in the experimental group compared with the results in rats trained in avoidance against the background of the action of cobalt salt and piracetam (Fig. 4). This can be explained by the fact that when ascorbic acid is added to piracetam solutions containing heavy metal salts, significant changes in the UV spectra of the corresponding solutions are noted. Ascorbic acid, chemically acting as the strongest reducing agent, is capable of being oxidized into dehydroascorbic acid and, thus, together with it represents a redox system. Reacting with a heavy metal salt, ascorbic acid thereby neutralizes its catalytic effect on the structure of piracetam, thereby preventing the appearance of structural forms of piracetam in the solution, which worsen the formation of CRAA [20, 21].

Thus, analyzing the combined effects of heavy metals, piracetam and ascorbic acid on the learning and memory of rats, we found an aggravation of the neurotoxic effect of metals in the

presence of nootropics. Ascorbic acid performs a protective function, reducing or completely neutralizing the negative neurotoxic effects of heavy metal. The obtained data revealed the theoretical and practical need for further study of the combined effect of neurotropic drugs and heavy metal salts on the central nervous system.

Conflicts of Interest: The authors declare no conflict of interest.

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Article

Features of vestibular function in patients with sensorineural deafness of vascular origin

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Abstract: *Objective*: to study the features of vestibular dysfunction in patients with sensorineural hearing loss of vascular origin, depending on the degree of discirculation in the main vessels of the head.

Metods. We examined 60 patients with various degrees of sensorineural hearing loss with circulatory disorders in the vertebrobasilar system (VBS), including 36 (60%) women and 24 (40%) men. The average age of the surveyed was 49.9±1.89 years. All patients underwent audiometry in an extended frequency range up to 20 kHz, the study of acoustic stem evoked potentials, acoustic reflexometry. A caloric test was used to study experimental vestibular reactions, and the results were recorded using computerized electronystagmography. *Results*. According to the otoneurological examination, the patients were divided into 3 subgroups. Peripheral cochleovestibular syndrome (PCVS) was diagnosed in 14 (23%) patients, central cochleovestibular syndrome (CCVS) in 19 (32%), and combined cochleovestibular syndrome (CVS) was diagnosed in 27 (45%) patients. In the analysis of complaints presented by patients with SHD of vascular origin, the combined complaints of hearing deafness, tinnitus and neurological symptoms (headaches, amnesia, paresthesia, fatigue, etc.), as well as dizziness and neurological symptoms, significantly prevailed compared with individual complaints of hearing loss or dizziness ($p < 0.05$). An analysis of the asymmetry of the pathological process on the right or left side did not reveal significant differences, however, the proportion of patients with bilateral lesions in the subgroup with CCVS was significantly higher. If vestibular nystagmus is an unconditioned stem reflex, then optokinetic nystagmus is a product of the activity of the cerebral cortex and occurs with the active participation of the patient himself in the process of research.

Conclusion. The obtained data were compared with the structural changes and hemodynamic parameters in the blood of vertebral arteries (VA) and internal carotid arteries (ICA), as well as magnetic resonance imaging of the brain (MRI).

Keywords: vertebral-basilar insufficiency, computer electronystagmography, cochleovestibular syndromes.

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1. Introduction

According to both domestic and foreign authors, more than 70% of all auditory and vestibular disorders are vascular origin [1, 2, 3]. Vestibular disorders can be the first manifestation of circulatory insufficiency in the vertebrobasilar system (VBS), therefore it is important to identify early auditory and vestibular symptoms characteristic of vertebrobasilar insufficiency (VBI).

The main clinical manifestations of VBI are coordination disorders, dizziness, and hearing disorders, which significantly limit the ability to work and hinder social adaptation [4, 5].

The frequency of dizziness in patients with VBI, according to various data, ranges from 50-90%, and 88.4% of dizziness is non-systemic [6, 7, 8]. Pathological changes in horizontal optokinetic nystagmus are also among the most common symptoms in patients with vertebrobasilar insufficiency [10].

Objective: to study the features of vestibular dysfunction in patients with sensorineural hearing loss of vascular origin, depending on the degree of discirculation in the main vessels of the head.

2. Patients and Methods

We examined 60 patients with various degrees of sensorineural hearing loss with circulatory disorders in the vertebrobasilar system (VBS), including 36 (60%) women and 24 (40%) men. The average age of the surveyed was 49.9±1.89 years. The duration of the disease averaged 12.8±1.75 years. The control group included 18 otologically healthy individuals, 10 (58.8%) women and 7 (41.2%) men. The average age of the surveyed in the control group was 24.33±1.86 years. Due to the presence of inter-age difference between the main and control groups, a correction was made for the involutionary process (the presence of such a range of age differences makes the results of the study incomparable). Age-related hearing loss - presbycusis and static disorders - presbyastasis, characteristic of the elderly, are due to involutional processes in the auditory and vestibular analyzers, general age-related changes in the body corresponds to the average age of the control group presented in the study[11].

All patients underwent audiometry in an extended frequency range up to 20 kHz, the study of acoustic stem evoked potentials, acoustic reflexometry. A caloric test was used to study experimental vestibular reactions, and the results were recorded using computerized electronystagmography (ENG).

The data obtained were compared with structural changes and hemodynamic parameters of blood flow in the vertebral (VA), internal carotid arteries (ICA) recorded using ultrasound methods for studying blood flow (doppler ultrasound, ect), as well as with the brain magnetic resonance imaging (MRI).

3. Results

According to the otoneurological examination, the patients were divided into 3 subgroups. Peripheral cochleovestibular syndrome (PCVS) was diagnosed in 14 (23%) patients, central cochleovestibular syndrome (CCVS) in 19 (32%), and combined cochleovestibular syndrome (CVS) was diagnosed in 27 (45%) patients.

In the analysis of complaints presented by patients with SHD of vascular origin, the combined complaints of hearing deafness, tinnitus and neurological symptoms (headaches, amnesia, paresthesia, fatigue, etc.), as well as dizziness and neurological symptoms, significantly prevailed compared with individual complaints of hearing loss or dizziness ($p < 0.05$). (Fig.1)

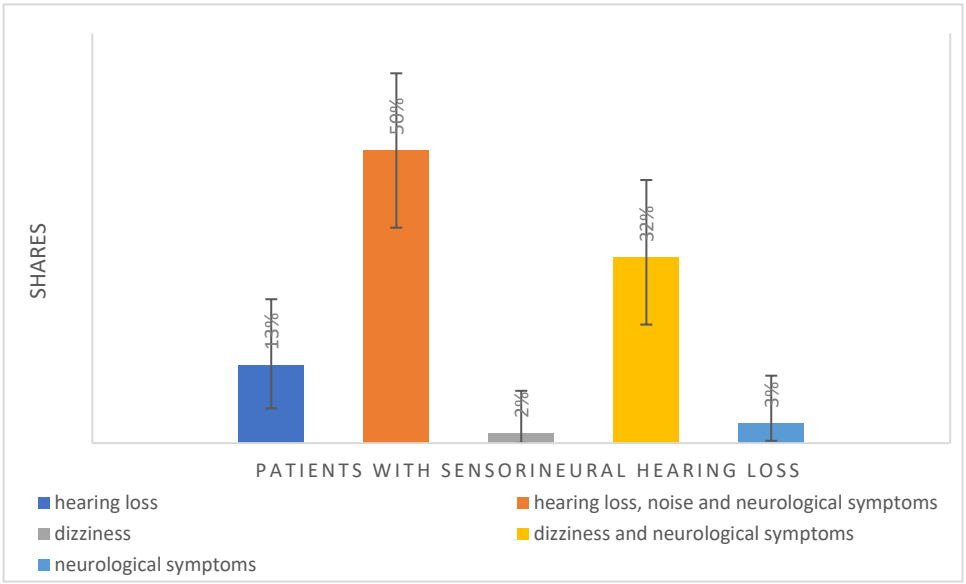

Figure 1. Distribution of complaints in patients with sensorineural hearing deafness. p<0.05

An analysis of the asymmetry of the pathological process on the right or left side did not reveal significant differences, however, the proportion of patients with bilateral lesions in the subgroup with CCVS was significantly higher (Fig. 2)

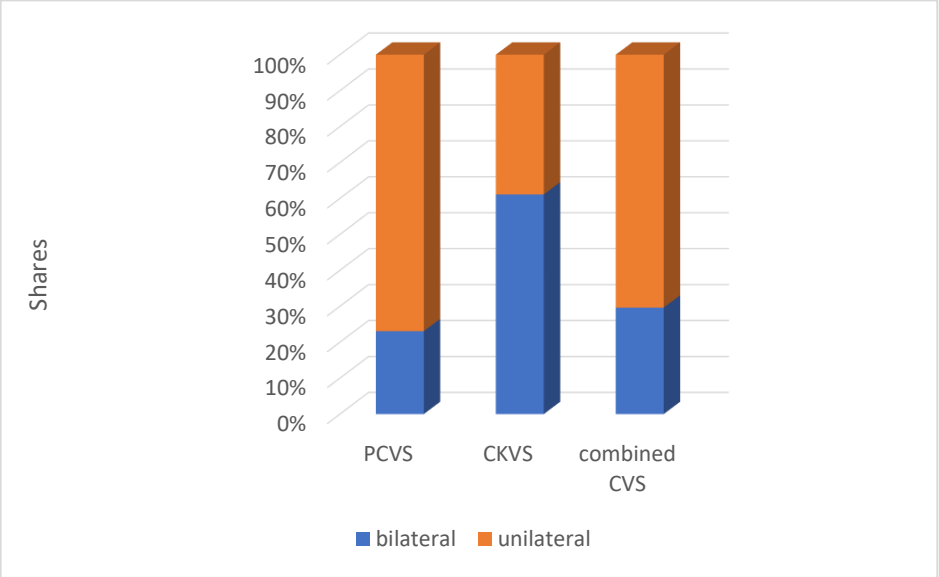

Figure 2. Distribution of patients with sensorineural hearing deafness depending on the side of the lesion and the type of CVS. p<0.05

In our study, dizziness was noted in 47 (78.3%) patients, in 32 (53.3%) patients it was non-systemic and in 15 (25%) - systemic. In 13 (21.7%) cases, dizziness was absent.

Non-systemic vertigo significantly prevailed in the subgroup of patients with combined and central CVS, and systemic vertigo in patients with PCVS (Table 1).

Table 1. Distribution of patients with sensorineural hearing deafness of vascular origin depending on the type of dizziness. (The table should provide statistical indicators - n (P ± m) (*p< 0,001).

Cochleovestibular syndromes	Dizziness			Total
	no	non-systemic	systemic	
Peripheral cochleovestibular syndrome (n=14)	5(36%)*	-	9 (64%)*	14
Central cochleovestibular syndrome (n=19)	4(21%)*	15 (69%)*	-	19
Combined cochleovestibular syndrome (n=27)	4 (16%)*	17 (63%)*	6 (22%)*	27
Total	13 (22%)	32 (53%)	15(25%)	60

Spontaneous nystagmus was recorded in 42 (70%) patients, of which in 29 (48.3%) cases it was unilateral and in 13 (21.7%) cases it was bilateral. (Table 1).

Table 2. Distribution of patients with sensorineural hearing deafness of vascular origin depending on the type of dizziness. (The table should provide statistical indicators - n (P ± m) (p<0, 01*).

nystagmus	PCVS	CKVS	Combined
Absent	5 (35,7)	7 (36,8%)	6 (22,2%)
Unilateral	8 (57,1%)	7 (36,8%)	14 (51,9%)*
Bilateral	1 (7,1%)	5 (26,3%)	7 (25,9%)

With PCVS, unilateral nystagmus was diagnosed in most cases, which indicates the interest of one of the labyrinths. In patients with CCVS and PCVS, spontaneous nystagmus had both one and two-sided direction, which indicates the involvement in the pathological process of the vestibular nuclei of the IV ventricle bottom and vestibulo-oculomotor connections in the posterior longitudinal bundle[9].

If vestibular nystagmus is an unconditioned stem reflex, then optokinetic nystagmus is a product of the activity of the cerebral cortex and occurs with the active participation of the patient himself in the process of research.

In cases of impaired blood supply to the VBI, optokinetic nystagmus can also be subjected to pathological changes.

Violation of optokinetic nystagmus was noted by us in 20 (33.3%) patients.

In the PCVS subgroup, no pathological changes were recorded; in the subgroups with CCVS and combined CVS, disturbances of optokinetic nystagmus were detected, which significantly differed from the subgroup with PCVS. These pathological changes indicate a deep CNS lesion both at the subtentorial and supratentorial levels in the two marked subgroups (Table 3).

Table 3. Distribution of disturbances in optokinetic nystagmus depending on the type of PCVS. (in the table, statistical indicators should be given - n (P ± m) (p‹0,01).

optokinetic nystagmus	PCVS	CKVS	Combined
not violated	14 (100,0%)	10 (52,6%)	16(59,3%)
violated	-	9*(40,7%)	11*(40,7%)

Computed electronystagmography was performed in 51 patients with sensorineural hearing deafness: 13 patients with PCVS, 15 patients with CCVS, and 23 patients with combined CVS. The quantitative and qualitative components of spontaneous and experimental vestibular reactions were analyzed. A bithermal caloric test was used to stimulate the vestibular analyzer.

When studying caloric nystagmus, its frequency (Freq), latency until the onset of the climax (Cul N), slow phase velocity (SPV), amplitude (Ampl), total amplitude (T Ampl) were recorded during calorization on the right (R) and left (L) hot (44°C) and cold water (20°C).

All of the above parameters were evaluated for the main, horizontal component of the experimental caloric nystagmus.

A qualitative assessment was also carried out: the presence of a vertical component, monooculars, and vestibulo-vegetative and somatosensory reactions.

According to the results of the data analysis from the study of the frequency of horizontal spontaneous nystagmus to the right (SNyD) and to the left (SNyS) (where are these frequency indicators?), see Table 4, it can be argued that there are statistically significant differences (p‹0.01) both between the normal group and the group SNHD in general and within the SNHD group with a tendency to increase the frequency of spontaneous nystagmus in patients with CCVS (p‹0.05) (Table 4).

Table 4. Frequency of spontaneous horizontal nystagmus in groups of patients with sensorineural hearing loss of vascular origin and in the control group (p‹0,01).

The frequency of spontaneous horizontal nystagmus	I.Control group (n=18)	II.Group of patients with sensorineural hearing loss in general (n=51)	Group of patients with sensorineural hearing loss depending on the type KVS.		
			III. PCVS (n=13)	IV. CKVS (n=15)	V. Combined KVS. (n=23)
SNyD	8±1,7	16,6±1,6 I-II	16,9±2,0 I-III	15,7±3,7 I-II	16,8±2,5 I-V
SNyS	9,2±2,3	16,9±1,7 I-II	14,0±2,5 I-III	21,0±3,5 I-II, III-IV	16,3±2,7 I-V

Hidden vertical spontaneous nystagmus was detected in 7 patients, including: 3 patients with CCVD and 4 patients with combined CVD.

In all cases, vertical nystagmus was combined with horizontal nystagmus. Isolated vertical nystagmus was not recorded.

In the analysis of experimental vestibular reactions in the group of patients with SNHD as a whole, compared with the normal group, there is a significant increase in the frequency of caloric nystagmus (no data), as well as in the total amplitude during stimulation with hot and cold water

(p<0.01). There was an increase in the latent period and the rate of the slow phase of the experimental nystagmus (no data), see Table 5 with cold water stimulation (p<0.05) (Table 5).

In the subgroup of patients with PCVS, there was a significant increase in the frequency (no data) of experimental nystagmus during stimulation with hot water on both sides and cold water on the right (p<0.05), as well as an increase in the latent period during calorization with cold water against the ba CKVS CKVSground of a decrease in the amplitude of nystagmus (no see tab. 6 for data). Other CENG parameters did not significantly differ from the normal group or were less (Table 6).

Table 5. Comparative characteristics of CENG indicators in patients with sensorineural hearing loss of vascular origin and in the control group (p<0,05, ** p<0,01, *** p<0,001).

Indicators of computer electronystagmography	Control group (n=18)		Vascular Genesis Group (n=51)	
	AD	AS	AD	AS
Freq 44°C, N/30 sec.	37,6±2,9	39,7±3,4**	37,0±2,5	44,5±3,2**
Cul N 44°C, sec.	29,7±5,8	21,1±4,1	30,5±3,6	25,6±3,2
Ampl 44°C, uV	138,4±8,6***	145,3±12,9***	82,1±7,4***	82,0±6,5***
SPV 44°C,º/ sec.	7,45±0,61	11,6±1,6	9,3±0,8	10,2±1,2
T Ampl 44°C, °	321,0±58,1*	449,1±90,2	341,1±40,8*	531,4±67,6
Freq 20°C, N/30 sec.	43,2±3,1**	43,4±3,8*	54,7±3,1**	50,9±3,1*
Cul N 20°C, sec.	12,8±3,8*	23,7±6,3	21,0±3,3*	23,8±2,6
Ampl 20°C, uV	167,2±10,5	176,6±12,6*	114,1±10,6	96,4±6,5*
SPV 20° C,º/ sec.	13,4±2,1	15,4±2,4	15,1±2,0	12,2±1,1
T Ampl 20°C,°	681,6±149,2	616,0±146,2**	670,0±73,7	622,0±75,5**

Table 6. Comparative characteristics of CENG indicators in patients with sensorineural hearing loss of vascular origin with PCVS and the control group (* p<0,05, ** p<0,01,*** p<0,001)

Indicators of computer electronystagmography	Control group (n=18)		PCVS (n=13)	
	AD	AS	AD	AS
Freq 44°C, N/30 sec.	37,6±2,9*	39,7±3,4*	42,2±11,7*	43,5±4,6*
Cul N 44°C, sec.	29,7±5,8	21,1±4,1	32,1±7,4	22,1±4,6
Ampl 44°C, uV	138,4±8,6	145,3±12,9***	78,5±11,7	83,9±14,6***
SPV 44°C,º/ sec.	7,45±0,61	11,6±1,6	7,4±0,8	10,2±2,1
T Ampl 44°C, °	321,0±58,1	449,1±90,2	323,9±66,9	430,1±105,2
Freq 20°C, N/30 sec.	43,2±3,1*	43,4±3,8	50,1±4,4*	45,9±5,2
Cul N 20°C, sec.	12,8±3,8*	23,7±6,3	22,0±5,8*	25,5±6,7
Ampl 20°C, uV	167,2±10,5	176,6±12,6**	133,6±36,7	104,8±15,9**
SPV 20° C,º/ sec.	13,4±2,1	15,4±2,4	14,6±5,7	10,8±1,7
T Ampl 20°C,°	681,6±149,2*	616,0±146,2*	419,3±85,9*	440,5±117,0*

An increase in the latent period during calorization with cold water, which is a more powerful stimulus of the vestibular analyzer than hot water, indicates a violation of the functional state of the vestibular analyzer and the presence of the "vestibular recruitment" phenomenon.

When analyzing qualitative indicators, the vertical component was detected only in one patient of the subgroup, and the monoocularity of the experimental vestibular reaction was not recorded.

Vestibulo-vegetative reactions and sensory reactions were expressed moderately and proceeded harmoniously in 11 (84.6%) patients with normoreflexia of vestibular reactions. In two cases of hyperreflexia (15.4%), vestibulo-vegetative reactions and sensory reactions proceeded rapidly, but harmoniously.

Thus, in patients with PCVS, all components of the experimental vestibular reaction proceeded in the same direction, which is typical for damage to the peripheral part of the vestibular analyzer.

Considering the asymmetry of vestibular reactions, it can be noted that a significant predominance of asymmetry in the labyrinth was revealed compared to the predominance in the direction in 9 (69.2)% of 13 cases, more pronounced than in the normal group.

According to the brain MRI, focal lesions of the brainstem and subcortical regions were visualized only in 3 (21%) cases.

In the study of blood flow, the greatest changes were obtained in the VA system in the form of obstruction of blood flow in 8 (57.1%) cases, hypoplasia and non-linearity of the course - in 9 (64.3%). Violation was also detected in the ICA system, but only in 2 (14.3%) cases. Obstruction of venous outflow was recorded in 13 (-93%) patients.

Table 7. Comparative characteristics of CENG indicators in patients with sensorineural hearing deafness of vascular origin with CVD and the control group (* p<0,05)

Indicators of computer electronystagmography	Control group (n=18)		CKVS (n=15)	
	AD	AS	AD	AS
Freq 44°C, N/30 sec.	37,6±2,9	39,7±3,4*	35,6±6,2	54,4±4,8*
Cul N 44°C, sec.	29,7±5,8	21,1±4,1	43,4±8,1	27,6±7,1
Ampl 44°C, uV	138,4±8,6*	145,3±12,9	94,7±21,8*	90,2±14,3
SPV 44°C,º/ sec.	7,45±0,61*	11,6±1,6	9,1±1,6*	11,7±1,8
T Ampl 44°C, °	321,0±58,1	449,1±90,2	281,3±71,2	708,8±123,6*
Freq 20°C, N/30 sec.	43,2±3,1*	43,4±3,8	58,3±6,5*	56,0±7,5
Cul N 20°C, sec.	12,8±3,8*	23,7±6,3	24,2±7,9*	14,5±3,6*
Ampl 20°C, uV	167,2±10,5	176,6±12,6	115,5±12,4	103,6±12,8*
SPV 20° C,º/ sec.	13,4±2,1	15,4±2,4	16,0±3,1	12,0±2,0
T Ampl 20°C,°	681,6±149,2	616,0±146,2	724,4±130,0	583,7±143,7

When analyzing CENG data in patients with CCVS, a significant (p<0.05) increase in the amplitude, slow phase velocity and total amplitude on the right and the frequency of experimental nystagmus on the left (no data) during calorization with hot water, as well as the frequency of experimental nystagmus on the right and latency of the vestibular reactions on both sides during calorization with cold water (no data). The results obtained indicate an increase in vestibular excitability and involvement in the pathological process of the central parts of the vestibular analyzer (Table 7).

When analyzing qualitative indicators, the vertical component of the experimental nystagmus was recorded in 11 (73.3%) patients, monoocularity - in 6 (40%). Hyperreflexia of the vestibular experimental reaction was detected in 10 (66.7%) patients, normoreflexia - in 5 (33.3%) cases.

Vestibulovegetative reactions and sensory reactions proceeded disharmoniously, and mainly according to the subtentorial type in 12 (80%) cases and according to the supratentorial type in 3 cases (20%).

When analyzing the asymmetries of vestibular reactions in 75% of cases, a predominance in direction was revealed.

4. Discussion

Thus, in the subgroup of patients with CCVS, the central lesion of the vestibular analyzer with hyperreflexia and subtentorial nature of the experimental vestibular reactions prevailed.

Focal lesions of the brainstem were found in 16 (84.2%) patients with CCVS, and in the white matter of the brain in 8 cases (42.1%).

In the study of blood flow disorders, obstruction of blood flow in the VA was detected in 15 cases (78.9%), in the common carotid artery (CCA) in 5 (26.3%) cases, in the ICA - in 10 (52.6%) cases, and also ICA occlusion in 2 (13%). Difficulty in the venous outflow of their cranial cavity was recorded in 15 (78.9%) patients. Structural changes in the PA system in the form of hypoplasia, asymmetry of diameters and non-linearity of the course were detected in 11 patients (57.9%), in the CCA system in 4 (21.1%) and in the ICA system in 6 (31.6%), t .e. there are more gross changes in the system, not only in the VA system, but also in the CCA and the ICA.

In the case of combined CVS, a significant ($p<0.05$) increase in the amplitude of the experimental nystagmus and the speed of the slow phase was obtained during stimulation with hot water from both sides, as well as an increase in the frequency of experimental nystagmus during stimulation with cold water on the left. The vertical component was detected in 3 (11.5%) patients, monoocularity - in 14 (53.8%), hyperreflexia of vestibular experimental reactions - in 17 (65.4%) patients, which indicates the interest of the central department of the vestibular analyzer. In 6 (26%) cases, normoreflexia was noted.

Vestibulo-vegetative reactions and sensory reactions proceeded disharmoniously in 17 patients (74%), and mainly in the supratentorial type, peripheral type in 6 cases (26%).

According to MRI data, focal lesions of the brainstem were detected in 12 (44.4%) patients, in the white matter of the brain in 18 cases (66.7%), most often in the form of leukoaraiosis[12].

Difficulty in blood circulation in the VA system was detected in 19 (70.4%) patients of this subgroup, with a predominant decrease in blood flow of 50%-60% and unilateral occlusions in 3 patients (11%). In the CCA and ICA systems, stenoses were detected in 3 (11%) and 9 (33.3%) cases, respectively, and occlusions in 2 (7.4%) and 4 (14.8%) cases. Difficulty in venous outflow from the cranial cavity was present in most patents of this subgroup - 25 (92.6%). Path disturbance, hypoplasia, asymmetry of VA diameters were observed in 19 (70.4%) patients, CCA - 2 (7.4%), ICA - 6 (22.2%)[13].

Thus, the pathology of the VA and ICA systems with significant blood flow disturbances, as well as a pronounced obstruction of venous outflow from the cranial cavity, prevailed in patients with SNHD with concomitant CVS, compared with other studied subgroups.

5. Conclusions

Thus, in the subgroup of patients with CCVS, the central lesion of the vestibular analyzer with hyperreflexia and subtentorial nature of the experimental vestibular reactions prevailed.

Focal lesions of the brainstem were found in 16 (84.2%) patients with CCVS, and in the white matter of the brain in 8 cases (42.1%).

In the study of blood flow disorders, obstruction of blood flow in the VA was detected in 15 cases (78.9%), in the common carotid artery (CCA) in 5 (26.3%) cases, in the ICA - in 10 (52.6%) cases, and also ICA occlusion in 2 (13%). Difficulty in the venous outflow of their cranial cavity was recorded in 15 (78.9%) patients. Structural changes in the PA system in the form of hypoplasia, asymmetry of diameters and non-linearity of the course were detected in 11 patients (57.9%), in the CCA system in 4 (21.1%) and in the ICA system in 6 (31.6%), t .e. there are more gross changes in the system, not only in the VA system, but also in the CCA and the ICA[14].

In the case of combined CVS, a significant ($p<0.05$) increase in the amplitude of the experimental nystagmus and the speed of the slow phase was obtained during stimulation with hot water from both sides, as well as an increase in the frequency of experimental nystagmus during stimulation with cold water on the left. The vertical component was detected in 3 (11.5%) patients, monoocularity - in 14 (53.8%), hyperreflexia of vestibular experimental reactions - in 17 (65.4%) patients, which indicates the interest of the central department of the vestibular analyzer. In 6 (26%) cases, normoreflexia was noted[15].

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Thus, the pathology of the VA and ICA systems with significant blood flow disturbances, as well as a pronounced obstruction of venous outflow from the cranial cavity, prevailed in patients with SNHD with concomitant CVS, compared with other studied subgroups.

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Article

Dental implantation and radioprotectors after surgical treatment of head and neck oncology

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Abstract: Worldwide, head and neck cancer (HNC–Head Neck Cancer) is one of the most common types of neoplasms with an ever-increasing prevalence and mortality rate. The aim of the work is to improve the methods of restoring masticatory function in patients who previously received radiation and chemotherapy, dental implantation techniques with immediate loading and the use of radio detectors based on sodium deoxyribonucleate ("Coletex-Gel-DNA-L"). Materials and methods. The main group included 61 patients. For local radiation treatment, the drugs "Coletex-gel-DNA" and "Coletex-gel-DNA-L" were used. The control group included 77 patients who, for the prevention and treatment of radiation reactions of the mucous membranes of the oral cavity, used the classical method — applications of stone oils (olive, sunflower). Results. Of the 79 dental implants installed in patients of the second group, 17 implants were removed due to perimplantitis. The implant survival rate is 78.5% in the control group. Based on a follow-up period of 12 ± 2 months, the survival rate of implants was calculated in patients of the main and control groups. when using the drugs "Coletex-gel-DNA" and "Coletex-gel-DNA-L", there was a decrease in the frequency of radiation reactions of the III degree from 66.8 to 24.6% compared with the classical method of prevention, I and II degrees of radioepithelitis prevail, the results are reliable ($p < 0.01$). IV degree was not observed in any patient of both groups. Conclusion. The results obtained indicate the effectiveness of the use of the drugs "Coletex-gel-DNA" and "Coletex-gel-DNA-L" for the prevention and treatment of radiation reactions of the oral mucosa and pharynx in patients with malignant neoplasms of the oropharyngeal zone. In this regard, this drug may be recommended for use as a therapy to accompany radiation, chemoradiotherapy and combined treatment. The introduction into the practice of dentists, the algorithm of complex restoration of masticatory function in patients with a history of oncology is justified. It is possible to reduce side effects, improve the recovery process.

Keywords: one-stage implantation, radioprotector, bone tissue, tissue transplantation, intraoperative prosthetics, intraoperative implant positioning, beam system.

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1. Introduction

Worldwide, head and neck cancer (HNC–Head Neck Cancer) is one of the most common types of neoplasms with an ever-increasing prevalence and mortality rate. The survival rate of patients suffering from head and neck cancer depends on the type, stage and location of the cancer. More than 2/3 of patients are admitted to specialized hospitals with locally advanced forms of the disease. The sensitivity of tumors to radiation and drug effects, as well as the initial neglect of the process, led to the search for sufficiently effective methods of prevention and treatment of neoplasms and their consequences. Currently, promising areas for solving problems related to the treatment of patients with neoplasms are the use of unconventional dose fractionation regimes,

the use of various radiomodifiers, primarily hypoxic cell radiosensitizers, as well as radioprotectors, the search for effective combinations of radiation therapy and chemotherapy [1]. In radiotherapy, requirements are imposed on radioprotectors, namely: the need for differentiated protective action. It is necessary to ensure a high level of protection of healthy tissues and a minimum level of protection of tumor tissues. Such a distinction makes it possible to enhance the effect of a locally applied therapeutic dose of radiation on a tumor focus without serious damage to the healthy tissues surrounding it. The disadvantages of currently existing chemical radioprotectors include toxic side effects and a limited duration of action. All this served as the basis for the study of the radioprotective properties of low-toxic substances of biological origin, which would increase the overall stability of the body and resistance to infections, as well as stimulate the activity of the hematopoietic system [2].

As a result of antitumor treatment, patients experience a serious decrease in chewing function, which negatively affects their quality of life, since oral sanitation before radiation therapy consists in treating all teeth and removing teeth that may be sources of infection [3]. Partially toothless or completely toothless, they turn to the dentist with extensive anatomical deformities, which are often impossible to restore with conventional prosthetics, as it causes them serious inconvenience [4]. In addition, mucositis, tissue fibrosis and xerostomia are often observed in the oral cavity as side effects caused by radiation [5]. When planning post-oncological maxillofacial reconstructive treatment, such indicators as: time, localization, dose and technique of radiation therapy should be studied and taken into account [6]. In patients cured of HNC, dental implants are a good opportunity to restore masticatory function [7]. Modern requirements for the quality of life of patients motivate specialists to optimize protocols, primarily in time, and, of course, in the quality of life of the patient. There is a large group of patients who have previously undergone radiation and chemotherapy for malignancies in the maxillofacial region, to whom dental implantation is not recommended due to the low regenerative abilities of the tissues exposed to radiation. The tissues of the oral cavity are very susceptible to the effects of radiation and chemotherapy, which have a direct damaging effect on the tissues of the oral mucosa, salivary glands, bone tissue [8]. The main manifestations of dystrophic processes in the dental system are: suppression of vascularization, progressive hypoxia, bone resorption and atrophy, violation of its physiological restructuring, phenomena of osteoporosis, suppression of proliferation in healthy tissues.

Treatment of patients with cancer in the maxillofacial region is carried out using a combination of ablative surgery and radiation therapy. As a result of these methods of treatment, complications may occur, a decrease and change in the anatomical structure, a decrease in the rate of salivation, defects of soft and hard tissues leading to functional disability and aesthetic deformation, as a rule, require tissue transplantation with vascularized or non-vascularized flaps for their reconstruction. Strict selection criteria and soft-tissue autografts for enlargement and stabilization of soft tissues are favorable for the long-term survival of the implant. Accelerated rehabilitation (fast track surgery; enhanced recovery after surgery) is a group of simple measures that reduce morbidity, postoperative complications and accelerate postoperative rehabilitation, reducing hospital stay. [9]. It was first proposed in the 90s of the last century by H. Kehlet. According to the definition of H. Kehlet, it allows to reduce the stress reactions of the body and significantly reduce the time required for full recovery" [10]. Dental implantation occupies a leading position among modern methods of orthopedic treatment of patients with partial or complete absence of teeth. The success of dental implantation is ensured if the indications and generally accepted principles of implantation planning are observed, there are adequate clinical conditions, and a good level of oral hygiene [11]. The beam prosthetic structure was preferable to single structures in terms of retention and chewing ability [12]. Immediate surgical and orthopedic rehabilitation plays an important role in solving such complications [13]. The implantation protocol with intraoperative immediate prosthetics in the area of missing and removed teeth reduces the duration of treatment until the end of the surgical procedure and is most in demand among patients. An undeniable advantage is the ability to start using prostheses immediately after implantation surgery [14].

2. Objective

The improvement of the methods of restoring masticatory function in patients who previously received radiation and chemotherapy, dental implantation techniques with immediate loading and the use of radio detectors based on sodium deoxyribonucleate ("Coletex-Gel-DNA-L").

3. Materials and methods

Two groups of patients were included in the study. The main group included 61 patients. During radiation treatment, the drugs "Coletex-gel-DNA" and "Coletex-gel-DNA-L" were applied topically. The control group included 77 patients who, for the prevention and treatment of radiation reactions of the mucous membranes of the oral cavity, used the classical method — applications of stone oils (olive, sunflower).The main part was made up of able-bodied men over 50 years

old (70.6%).The majority (85.5%) of patients in both groups had stages III and IV of the disease.In 74.6% of patients, squamous cell carcinoma was detected during histological examination of the tumor, adenocarcinoma, lymphoma, myeloma, mucoepidermoid cancer were detected in 25.4%. The age of patients is from 37 to 60 years. The largest group consisted of patients aged 41 to 60 years, i.e. persons of working age. A standard dental examination was performed. Concomitant diseases, bad habits (smoking, alcohol abuse) were determined. Both groups of patients were evaluated according to the classification of the American Society of Anesthesiologists (ASAIII classification). During the examination of the oral cavity, attention was paid to the type of bite, the number of teeth, carious and non-carious lesions. The presence of dentures and their quality, the condition of existing fillings were recorded. The hygienic condition of the oral cavity was assessed by the Fedorov–Volodkina method. 175 implants were installed in patients, finally supporting 24 beam structures in the 1st group of patients and single and bridge-shaped structures in the 2nd group of patients. At the first stage of the work, an assessment of the stability of dental implants in bone tissue, an assessment of the condition of soft tissues was carried out.

1 group of patients (main group) who had previously received radiation and chemotherapy and were in remission for more than 6 months, in whom the restoration of masticatory function was carried out by means of simultaneous installation of dental implants with immediate loading of orthopedic construction using hydrogel radio detectors based on sodium deoxyribonucleate ("Coletex-Gel-DNA-L")/

2 group of patients (control group), who had previously received chemoradiotherapy and were in remission for more than 6 months, who underwent dental implantation according to a two-stage protocol without the use of radioprotectors.

The distribution of patients by groups is shown in table 1

1st group	61 pers.	44,2 %
2nd group	77 pers.	55.8 %
Total	138 pers.	100 %

Table 1. Distribution of patients into groups

All patients underwent RT on Clinac C2100 linear electron accelerators in the bremsstrahlung mode with a photon energy of 6 MV. The classical mode of dose fractionation was used (GENUS 2 Gy, 5 fractions per week). The scope of irradiation included a primary tumor detected before the start of treatment, or a clinically determined tumor, and regional lymph nodes. The primary tumor and lymph nodes of levels I and II were irradiated through oncoming lateral fields to a total focal dose (TFD) of 44-46 Gy with brain screening. The middle and lower groups of lymph nodes (level III, IV, V, VI) were irradiated through the anterior direct field to TFD 44-46 Gy. With radical radiation treatment, after reaching TFD 44-46 Gy, the size of the fields was reduced, limited by the volume of the primary tumor and affected lymph nodes detected before treatment. With radical RT, local irradiation (boost) continued up to TFD 68-70 Gy, with postoperative — up to 50-64 Gy, with preoperative RT, TFD was 44-46 Gy.

At the V. N. Orekhovich State Research Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences, studies which were conducted showed that the hydrogel used is characterized by the presence of particles of the nanometer range with a diameter of 20 to 250 nm (up to 90%), large particles of more than 1000 nm were no more than 3% (the analysis was carried out by photon-correlation spectroscopy on device N5 BeckmanCoulter; X = 648 nm) The gel has a yellow-green color characteristic of natural algae, has no specific taste and smell and is available in sterile packages after gamma sterilization of 100 ml.

The use of radio detectors based on sodium deoxyribonucleate ("Coletex-Gel-DNA-L"). Sodium alginate, which is the basis of the gel, is a natural biopolymer obtained from brown algae rich in trace elements, helps to reduce bleeding, cleanses the wound, accelerates tissue repair. It contains more than 90% of nano-meter range particles. In addition to the therapeutic effect, sodium alginate performs the functions of a carrier of a finely dispersed form of a medicinal substance and a protective colloid to prevent aggregation of drug particles. The gel envelops the mucous membrane, lubricates it and stays on this surface. Gradually, a drug is released from the gel, which has its inherent therapeutic effect. The rate of release of the drug is due to the rate of swelling of the gel. This process takes a long time, which makes it possible to attribute the "kolegel" to the therapeutic materials of prolonged action. Both the biopolymer base of the gel (sodium alginate) and the drug injected into it (derinat) have a positive effect. The gel base releases the medicine faster than the fat base, and the feeling of moisture in the mouth and pharynx persists longer.

In the preparation "Coletex-gel-DNA", the preparation "derinate sodium salt" (sodium deoxyribonucleate (Na-DNA)), approved by the Ministry of Health and Social Development of Russia

for widespread use, is impregnated into sodium alginate, which is an immunomodulator and antioxidant. The composition of the drug "Coletex-gel-DNA-L", in addition to sodium alginate and derinate, includes lidocaine for pain relief. Derinat is a universal metabolic modulator that has a non—specific general biological stimulating effect on all organs and tissues, normalizes the immune status, enhances tissue regeneration, stabilizes hematopoiesis.

Patients of the main group from the first day of RT independently applied the preparations "Coletex-gel-DNA" and "Coletex-gel-DNA-L" to the mucous membrane of the oral cavity 3 times a day for 5 ml for 40 minutes after preliminary sanitation of the oral cavity, periodically redistributing it with the tongue along the oral mucosa.

In the control group, patients from the first day of RT applied olive or sunflower oil 3 times a day after preliminary sanitation of the oral cavity.

All patients before the start of RT were informed about the occurrence of local side effects from the oral mucosa during RT and received recommendations on oral care and nutrition. Patients from the first day of treatment began rinsing the oral cavity with solutions of chamomile, furacilin. Antibacterial therapy was not used. Spicy, salty, hot, cold food, carbonated drinks were excluded from the diet.

Dental treatment of patients was carried out according to a certain algorithm (figure 1)

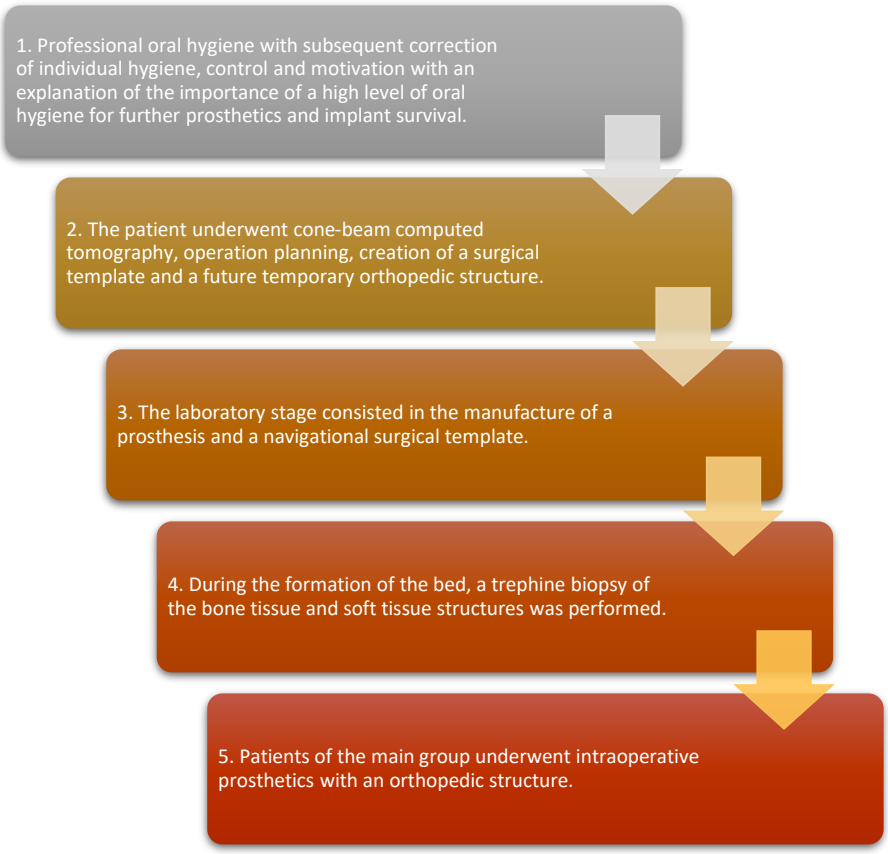


Diagram 1. Algorithm of dental treatment of patients after radiation therapy.

4. Results and discussion

Of the 79 dental implants installed in patients of the second group, 17 implants were removed due to perimplantitis. The implant survival rate is 78.5% in the control group. The evaluation of implant survival in group I and group II patients during 12 ± 2 months of follow - up is presented in diagram 2.

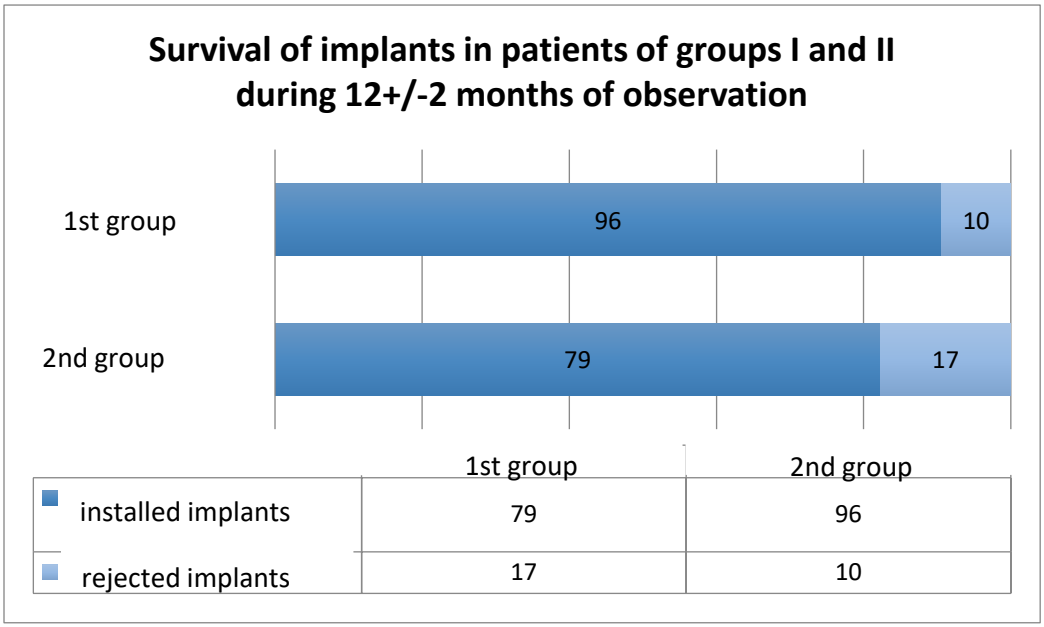
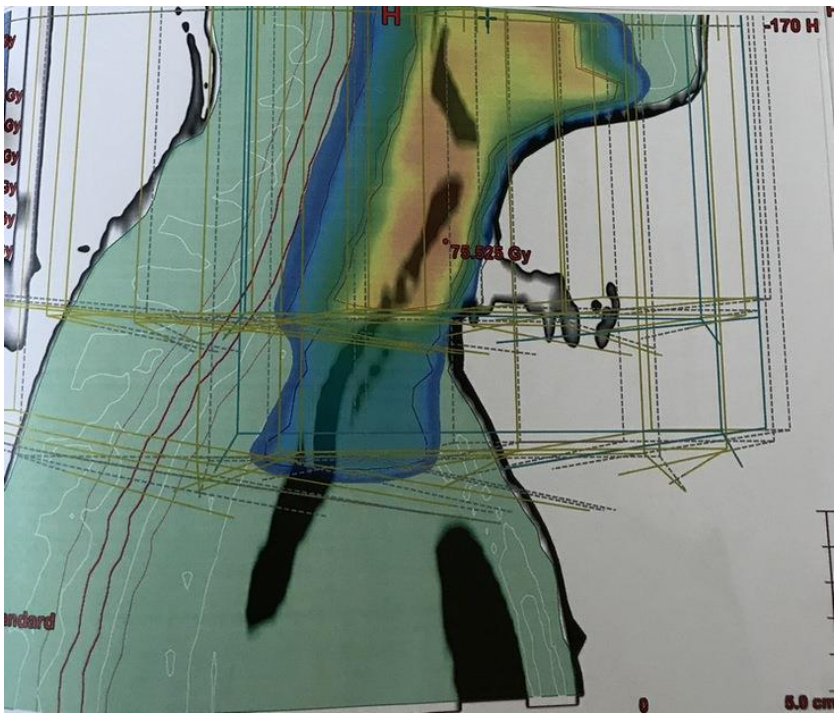


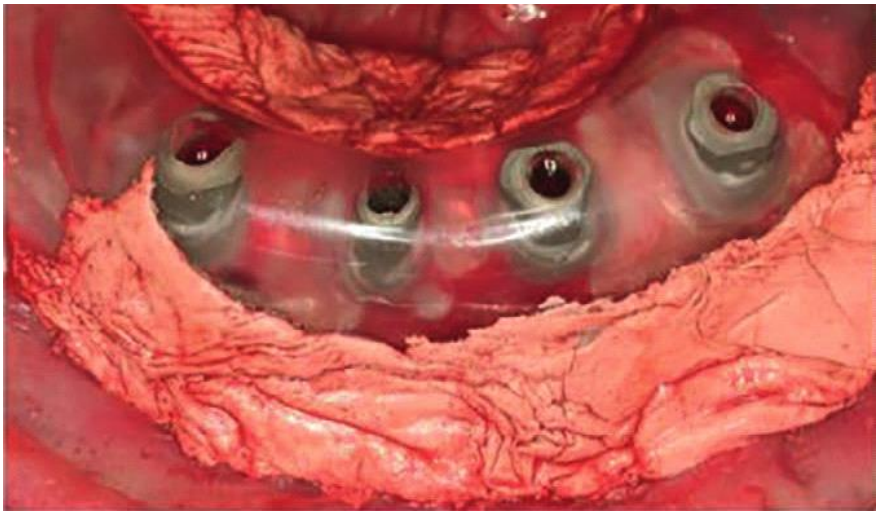
Diagram 2. Implant survival in group I and group II patients during 12 ± 2 months of follow-up.

Clinical example: Patient K., 47 years old. Diagnosis: laryngopharyngeal cancer, condition after combined treatment in 2016. Radiation therapy of TFD 38 G was performed (Field 1 – 14.3cmx10.3cm, Field 2 - 15.0 cm x 10.6 cm, setup-0 – 12.9cmx 13.5cm) (Fig. 21), two courses of chemotherapy according to the scheme: Taxotere 150 mg, Cisplatin 150 mg, 5-fluorouracil 8000 mg.

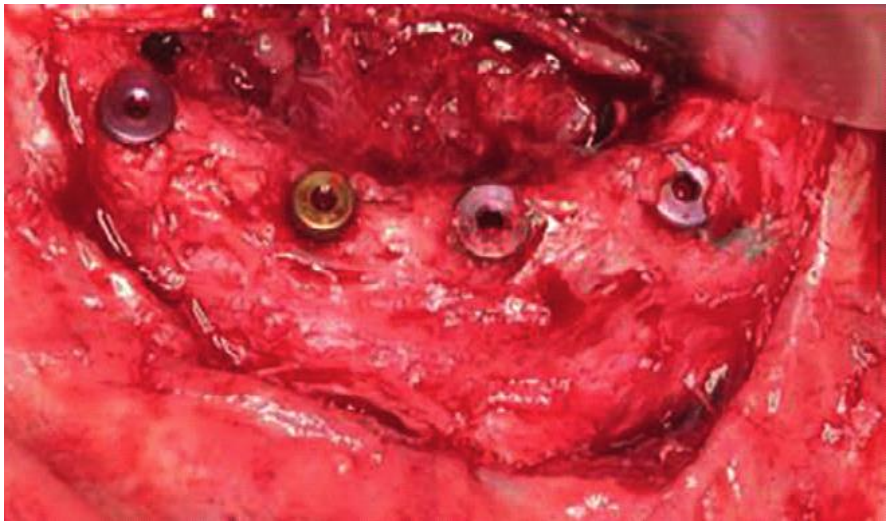
A treatment plan has been drawn up: - consultation with an oncologist; CBCT to determine the volume of bone tissue in the alveolar part of the lower jaw; study of the radiological map (in order to obtain information about the tissues of the oral cavity that have fallen into the direct focus of radiation and cannot be used to place dental implants) (Fig. 21);- surgery to install four dental implants on the lower jaw with intraoperative load; for two weeks of application with a hydrogel radioprotector based on sodium deoxyribonucleate with lidocaine.



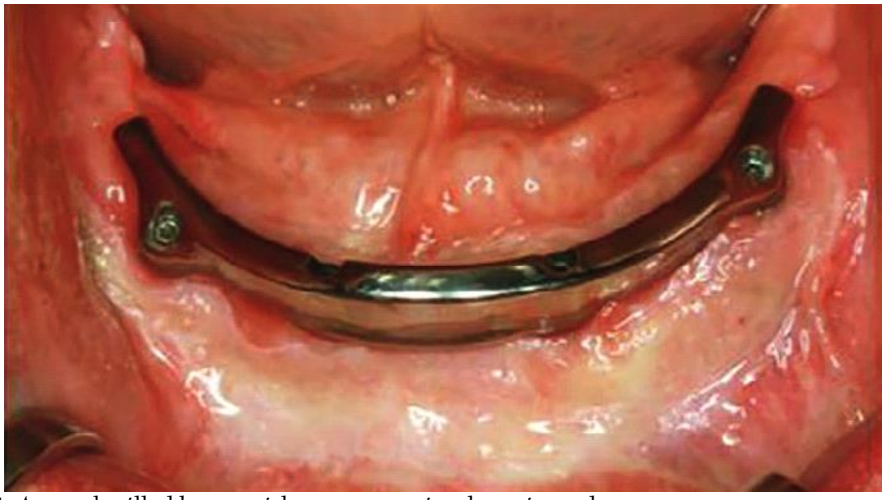
Picture 1. Patient K. Radiation map. The irradiated area is the larynx.



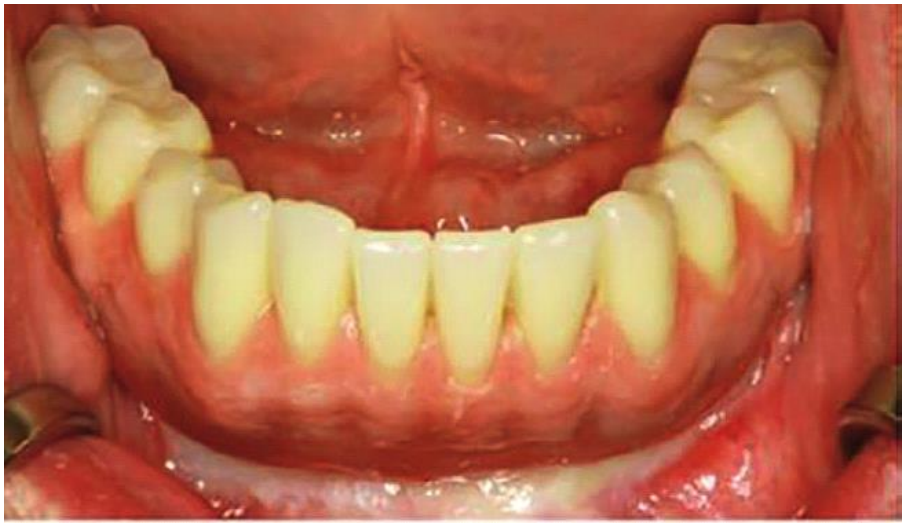
Picture 2. Installation of the operational template.



Picture 3. 4 implants are installed in the intermental space of the lower jaw.



Picture 4. A metal milled beam with support on implants is made.



Picture 5. The final view of the prosthesis on the lower jaw, fixed on the beam.

We recorded changes in the mucous membrane of the oral cavity and pharynx. The results obtained were compared with the results of the control group, which used standard prevention of radiation reactions of the oral mucosa and pharynx (olive, sunflower oil) during radiation treatment. When using "Coletex-gel-DNA" and "Coletex-gel-DNA-L", allergic reactions were not detected in any patient.

Based on a follow-up period of 12 ± 2 months, the survival rate of implants in patients of the main and control groups was calculated.

Patients of the first group: out of 96 installed dental implants, 7 implants were removed due to perimplantitis. The survival rate of implants in the first group was 89.6% Table 2. In the main group, the disintegration of implants is associated with non-compliance with the recommendation (smoking, poor oral hygiene). In the control group, the disintegration of implants was manifested at the stage of installing gum shapers and fixing single and bridge-shaped structures based on dental implants.

Data on the condition of the soft tissues around the implant in comparison with the main and control groups: when using hydrogel radioprotectors based on sodium deoxyribonucleate with lidocaine, there was a decrease in the severity of pain and edema, as well as a reduction in tissue regeneration.

Based on the results obtained, it can be noted that when using the drugs "Coletex-gel-DNA" and "Coletex-gel-DNA-L", there is a decrease in the frequency of radiation reactions of the III degree from 66.8 to 24.6% compared with the classical method of prevention, I and II degrees of radioepithelitis prevail, the results are reliable ($p < 0.01$). Grade IV was not observed in any patient of both groups.

The degree of severity of radiation reactions was assessed depending on the timing of their occurrence. Based on these data, it can be concluded that when using the drugs "Coletex-gel-DNA" and "Coletex-gel-DNA-L", the period before the occurrence of radiation reactions of the oral mucosa and pharynx increases by an average of 8 days ($p < 0.05$).

The degree of severity of radiation reactions was assessed depending on the dose of RT. As the TFD increases, the advantage of using a gel compared to the classic option of preventing radiation reactions is noted. Thus, when summing up TFD 68-70 Gy, the frequency of grade III radioepitheliitis significantly decreases from 90.4 to 20.0% ($p < 0.05$), which is important, since 65.6% of the patients included in our study received RT according to the radical program. All patients of the main group managed to perform RT without interruption, in the control group 63.6% (49 patients) had a forced break in treatment, the results were reliable ($p < 0.05$).

5. Conclusion

The use of the drugs "Coletex-gel-DNA" and "Coletex-gel-DNA-L" significantly reduces the severity of radiation reactions of the oral mucosa and pharynx of the III degree from 66.8 to 24.6% compared with the classical method of preventing these reactions. When using the drugs "Coletex-gel-DNA" and "Coletex-gel-DNA-L", the continuity of the RT course is reliably ensured, which increases locoregional control. The frequency of grade III radioepithelitis significantly decreases from 90.4 to 20.0% when summing up TFD 68-70 Gy in patients who used the drugs "Coletex-gel-DNA" and "Coletex-gel-DNA-L". The period of the patient's stay in the hospital is reduced by an average of 10 bed days.

Author Contributions*:* Research concept and design, editing - V.A. Put. Collection and processing of material, writing the text - D.V. Anisimov. Collection of material - V.V. Arishkova. Processing and collection of material - I.I. Tarba.

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Article

The use of radio wave scalpel "Surgitron" in the surgical treatment of the outer ear neoplasms

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Abstract: The number of ENT organs diseases continues to grow, and therefore the problem of combating these diseases has been and remains relevant in otorhinolaryngology. The least studied of all the ENT organs neoplasm are ear tumors. *Aims*: to increase the efficiency of surgical treatment of neoplasms of the outer ear using a radio wave scalpel "Surgitron". *Patients and Methods*. The work is based on the results of treatment of 230 patients (146 in the main and 84 in the control groups) with tumor-like formations, benign and malignantouter ear tumors. *Results*. The first place in the structure of ear neoplasms in the main group was occupied by tumor-like formations - 58 patients (40%), benign tumors were somewhat less common - 48 patients (33%), and even less often - malignant neoplasms (40 patients, 27%). Most often, the auricle neoplasms were removed without the underlying cartilage (in 60 patients; 56.6%). Limited tumors (I-II stage) were removed under local anesthesia with 1% solution of novocaine with the addition, in the absence of contraindications, 5 drops of 0.1% solution of adrenaline per 10 ml of novocaine. After detachment of the tumor with skin and perichondrium from the underlying cartilage, an incision was made using a Surgitron radio wave scalpel, after which the tumor was removed within healthy tissues without cartilage resection. A strip of healthy skin around a benign tumor should be at least 3 mm. The surface of the cartilage at the bottom of the wound was examined under an operating microscope. The cartilage undamaged by the tumor had a smooth, shiny surface. Bleeding during the operation was minimal, stopped with the help of Surgitron, in the coagulation mode. In 1 patient with senile keratosis, in which the neoplasm was localized on the anterior surface of the auricle, the tumor was removed with a section of cartilage tissue. *Conclusion*. The use of the radio wave scalpel "Surgitron" in surgical interventions for outer ear neoplasms can reduce the time of the operation, reduce blood loss to a minimum, the time of wound epithelialization and the length of the patient's stay in the hospital. Comparison of the number of recurrences according to the result of using a radio wave scalpel and the classical surgical method (for tumor-like formations - 12% and 24.2%, respectively, for benign tumors - 8.3% and 40%, for malignant tumors - 30% and 70%) indicates a high effectiveness of surgical treatment using "Surgitron".

Keywords: tumor-like formations, benign and malignant outer ear neoplasms, radio wave scalpel "Surgitron".

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1. Introduction

The number of ENT organs diseases continues to grow, and therefore the problem of combating these diseases has been and remains relevant in otorhinolaryngology. The least studied of all the ENT organs neoplasm are ear tumors.

Tumors and tumor-like formatios of the auricle and external auditory canal are represented by: congenital fistulas developing from the remains of the first branchial fissure; cysts and scars

after mechanical, chemical and thermal injuries; keloids, congenital and acquired nevi; senile hyperkeratosis; chronic nodular chondrodermatitis, atheromas; histiocytosis (eosinophilic granuloma); skin horn [1].

Quite rarely, auricle and external auditory canal benign tumors are encountered [2], characterized by a great variety of histological structure. In the first place among them are papillomas [3], less common are hemangiomas, osteomas, ceruminomas, fibromas, chondromas, and lipomas.

Malignant ear tumors account for up to 2% of all malignant tumors and from 5 to 12% of ENT organs tumors. Of these, the auricle accounts for 85%, the external auditory canal - 10% [4].The main methods treatment of patients with outer ear tumors is surgical.

One method that increases the effectiveness of such interventions is the use of a radio wave scalpel [5, 6, 7]. In the literature, there are single reports on the removal of ear cancer using a radio wave scalpel [8].

Aims: to increase the efficiency of surgical treatment of neoplasms of the outer ear using a radio wave scalpel "Surgitron".

2. Patients and Methods

The work is based on the results of treatment of 230 patients (146 in the main and 84 in the control groups) with tumor-like formations, benign and malignantouter ear tumors.

The first place in the structure of ear neoplasms in the main group was occupied by tumor-like formations - 58 patients (40%), benign tumors were somewhat less common - 48 patients (33%), and even less often - malignant neoplasms (40 patients, 27%). The distribution of patients depending on the histological structure and primary localization of the neoplasm is presented in Table 1.

Table 1. Comparative characteristics of the treatment effectiveness of the studied groups of patients with tumor-like formations, benign and malignant neoplasms of the external ear (N=230).

Parameter	Main group (N=146)	Control group (N=84)	Difference between groups (%)
Duration of surgery (min)	41	49	16
Intraoperative blood loss (ml)	49	86	43
Wound healing time (weeks)	3,0	3,8	21
Length of stay in hospital (days)	13	17	24

The patients were aged 20 to 80 years, of which 64 (43.9%) were men and 82 (56.1%) were women. The auricle was the primary localization of the formation in 81 (55.4%) patients, the external auditory meatus - in 65 (44.6%).

In the control group, as in the main group, the first place was occupied by tumor-like formations - 33 patients (39%), the second - benign tumors - 30 patients (36%), the third - malignant neoplasms - 21 (25%) patients. There were 49 (58%) women in the control group, 35 (42%) men.

The auricle turned out to be the primary localization of the neoplasm in 53 (63%) patients, the external auditory meatus - in 31 (37%) patients.

The study began with a thorough history taking. To resolve the issue of the nature of the tumor, it is very important to determine the duration of the disease. The development of tumor-like, benign neoplasms occur within a few years, malignant - within a few months. We determined the time and sequence of the appearance of the first signs of the disease, its duration and the sequence of appearance of the patient's complaints, we judged the primary localization and direction of tumor growth. Outer ear neoplasms are characterized by a constant increase in symptoms.

The auricle is available for examination by the patient and the doctor; therefore, neoplasms of this localization are detected much faster than tumors of the external auditory canal. In all 135 patients with ear tumors in both groups of patients, the first sign of the disease was the appearance of the tumor itself. As a rule, it appeared for no apparent reason.

External auditory canal neoplasms are inaccessible for direct examination and develop asymptomatically for a certain time. Due to the anatomical features of the external auditory canal, its innervation, and the fact that the tumor grows in confined spaces, one of the leading symptoms in these cases was pain (16 patients). Pain and itching were followed by serous or purulent discharge from the ear canal mixed with blood (16 patients). Increasing in size, the tumor obturates the auditory canal, hearing loss appears according to the type of sound conduction disorder (16 patients).

On palpation, pastosity or hardening of the soft tissues of the parotid region and neck on the side of the lesion, their pain and enlargement were determined.

Computer tomography (CT) and magnetic resonance imaging (MRI) were used to determine the boundaries of the neoplasm and decide on the extent of the surgical intervention.

Surgical interventions were performed in 106 patients with benign tumors and tumor-like formations of the auricle and external auditory canal.

In all operated patients, the intervention was performed using a radio wave scalpel "Surgitron". There were no contraindications for the use of the latter in our study.

3. Results

Most often, the auricle neoplasms were removed without the underlying cartilage (in 60 patients; 56.6%). Limited tumors (I-II stage) were removed under local anesthesia with 1% solution of novocaine with the addition, in the absence of contraindications, 5 drops of 0.1% solution of adrenaline per 10 ml of novocaine. After detachment of the tumor with skin and perichondrium from the underlying cartilage, an incision was made using a Surgitron radio wave scalpel, after which the tumor was removed within healthy tissues without cartilage resection. A strip of healthy skin around a benign tumor should be at least 3 mm. The surface of the cartilage at the bottom of the wound was examined under an operating microscope. The cartilage undamaged by the tumor had a smooth, shiny surface. Bleeding during the operation was minimal, stopped with the help of Surgitron, in the coagulation mode. In 1 patient with senile keratosis, in which the neoplasm was localized on the anterior surface of the auricle, the tumor was removed with a section of cartilage tissue. In this observation, it was not possible to produce hydraulic detachment of tissues (perchondrium).

Resection of the auricle was performed in 3 patients (2.9%) with a cutaneous horn that partially destroyed the cartilaginous tissue of the auricle.

In our observations, there were 11 patients with auricular hemangioma, in whom the histological examination was performed only after surgical intervention. Biopsy in such cases is associated with the risk of intense bleeding, since we are talking about branched pulsating hemangiomas.

Hemangioma was removed within healthy tissues using a Surgitron radio wave scalpel after the tumor was sutured with a double twist suture (from above, behind, in front of the tragus along the posterior wall of the external auditory canal, a through U-shaped suture through the cavum conchae). With diffuse cavernous hemangiomas and other vascular tumors, when the border of the pathological focus is fuzzy, it is better to increase the strip of healthy skin around the tumor, up to 5 mm or more. Removal of vascular tumors, as a rule, is accompanied by severe bleeding, which is stopped by Surgitron in the coagulation mode.

Benign tumors and tumor-like formations of the external auditory canal in 40 patients were removed endourally with a Surgitron radio wave scalpel. Benign neoplasms of the cartilaginous part of the external auditory canal were most often removed with the perichondrium under local anesthesia. In 2 patients, due to the prevalence of the process, the tumor was removed by behind-the-ear access.

Patients with outer ear cancer were divided into 2 groups of equal size: 20 patients (13.7%) each with basal cell and squamous forms. In 18 (45%) cases, the tumors were localized on the auricle, in 22 (55%) cases, in the external auditory canal.

Before surgery, all patients underwent a biopsy to verify the diagnosis, after which surgical interventions were performed using a Surgitron radio wave scalpel.

In the surgical treatment of patients with auricle neoplasms in I-II stages of prevalence, we used various types of resection. Wedge-shaped resection of the auricle was performed more often (in 15 patients); when the tumor occupied 1/3 or more of the auricle, the latter was completely removed (in 3 patients).

12 patients with a malignant tumor process in the membranous-cartilaginous region underwent resection of the external auditory canal. Surgical intervention was performed under endotracheal anesthesia using a radio wave scalpel "Surgitron". After surgical treatment, patients were sent for radiation therapy.

Patients with malignant tumor invasion into the parotid salivary gland (stage III-IV) underwent resection of the external auditory canal with resection of the parotid salivary gland (7 cases). In 3 patients, the tumor extended beyond the external auditory meatus into the temporomandibular joint, tympanic cavity, and temporal bone, and in one case it grew into the cranial cavity. These patients underwent resection of the temporal bone and articular process of the lower jaw. The radio wave scalpel in this group of patients was used to work with soft tissues and coagulate the postoperative cavity.

The data on surgical interventions for the outer ear neoplasms in the control group (N=84) were taken from the archive.

These patients underwent surgical interventions by the classical method (using a scalpel). In view of the fact that the types of operations are identical with those interventions that were performed in the main group, only their structure and analysis are given below.

In the control group, as in the main group, the most common surgical intervention on the auricle was the removal of a neoplasm without underlying cartilage (37 patients, 59%). A tumor was removed along with the underlying cartilage in 1 patient with senile keratosis. Ear resection (wedge-shaped) was performed in 2 patients (3%) about the skin horn.

Benign tumors and tumor-like formations of the external auditory canal were removed endourally in 22 cases (35%). In 1 patient with a ceruminoma with a widespread process, the tumor was removed by behind-the-ear access.

Patients with malignant tumors of the external ear, basal cell carcinoma (11; 13%) and squamous cell carcinoma (10; 12%) were also operated on using the classical surgical method. In 16 cases, the tumor was localized on the auricle, in 5 cases - in the external auditory canal.

All patients underwent biopsy prior to surgery to verify the diagnosis. Most often, a wedge-shaped resection of the auricle was performed (in 10 patients); the auricle was completely removed in 6 patients for the same indications as in the main group. 2 patients with a tumor process in the membranous-cartilaginous region underwent resection of the external auditory canal.

Patients in whom a malignant tumor had grown into the parotid salivary gland (there were 2 of them) underwent resection of the external auditory canal with resection of the salivary gland. In 1 patient, the tumor grew beyond the external auditory canal into the temporomandibular joint, tympanic cavity, and temporal bone; this patient underwent resection of the external auditory canal with resection of the articular process of the lower jaw and resection of the temporal bone.

When all the tumors were removed, due to the good blood supply to the external ear, intense bleeding was noted, which was stopped mechanically (tight tamponade) or by ligation of the bleeding vessel.

The study groups of the main (146 patients) and control (84 patients) belong to the same general population and there were no statistically significant differences between them in terms of age, gender, localization of the formation, stage of the tumor and its histological structure.

In each of the groups, we tried to determine the duration of the surgical intervention, intraoperative blood loss, the time of wound healing, and the time of the patient's stay in the hospital. Surgical intervention performed using the Surgitron radio wave scalpel allows to reduce blood loss by 43% and reduce the total duration of the operation by 16% compared to the classical surgical method of treatment.

During surgical intervention using the Surgitron radio wave scalpel, bleeding can be stopped with the help of a coagulator, which significantly reduces the amount of intraoperative blood loss (main group). Radio wave scalpel "Surgitron" is characterized by high ablasticity and minimal trauma, which allows to accelerate the process of wound healing by 21% and reduce the length of the patient's stay in the hospital by 24%.

All patients with ear neoplasms after surgical treatment with the help of a radio wave scalpel "Surgitron" we observed in dynamics.

Patients with tumor-like and benign tumors were examined once every 2 months for the first 6 months, once every 3 months for the second 6 months, and then once a year. Patients with malignant neoplasms require closer monitoring: in the first year - 1 time per month, the second - 1 time in 2 months, and then – once a year. The follow-up period of the last group of patients is at least 5 years.

In patients with tumor-like formations, relapses were noted in 7 (12%) cases. Atheromas recurred in 4 cases, keloid, senile keratosis and cutaneous horn - in one observation. 44 (76%) patients were observed without recurrence, the connection was lost with 7 patients.

In patients with benign neoplasms, relapses were noted in 4 (8.3%) cases: one recurrence of squamous papilloma and hemangioma, 2 relapses of ceruminoma. At the same time, after surgical treatment, relapses of benign ear tumors were observed in 33.5% of cases [2].

In stages I and II, a malignant auricle tumor was detected in 9 cases, in the external auditory canal - in 15 cases. In stages III and IV, malignant tumors were detected in 16 patients. The neoplasm originated from the auricle in 9 cases, and from the external auditory meatus - in 7 cases.

28 patients (70%) were observed without signs of recurrence and metastasis from 1 to 5 years. Relapses were detected and 12 patients (30%) were reoperated

4. Discussion

According to the results of our studies [9-14], relapses of tumor-like formations, benign and malignant tumors were observed in only 23 (15.7%) patients, confirming the effectiveness of the use of the Surgitron radio wave scalpel in this pathology.

Patients in the control group were called for examinations and a retrospective analysis of relapses of neoplasms was carried out at the same time as in patients of the main group.

In patients with tumor-like formations, relapses were noted in 8 (24.2%) cases. 17 (51.6%) patients were observed without signs of recurrence. Communication was lost with 8 (24.2%) patients. This is consistent with data obtained in other studies [15-19].

In patients with benign neoplasms, relapses were noted in 12 (40%) cases. No signs of recurrence were observed in 14 (47%) patients [19, 20]. Communication was lost with 4 patients (13%).

When localized on the auricle, the malignant tumor recurred in 11 (50%) cases, in the external auditory canal - in 4 (20%). 6 patients (30%) are observed without signs of recurrence and metastasis from 1 to 3 years [20-22]. Relapses were detected and 15 patients (70%) were operated on again.

5. Conclusions

Thus, the study of the features of the clinic and diagnosis of outer ear neoplasms showed that tumors of the auricle manifest themselves much faster than tumors of the external auditory canal. Diagnosis requires careful history taking and examination of the ear and parotid region; at the same time, special attention should be paid to subtle symptoms of the disease. When the tumor becomes available for inspection, and the symptoms are obvious, it is easy to make a diagnosis, but it is difficult to treat the patient and hope for good treatment results. Surgical intervention has been and remains the main method of treating patients with tumors and tumor-like formations of the external ear, and the results of treatment of these patients depend on the duration of the disease, the initial location, extent and histological structure of the tumor.

The use of the radio wave scalpel "Surgitron" in surgical interventions for outer ear neoplasms can reduce the time of the operation, reduce blood loss to a minimum, the time of wound epithelialization and the length of the patient's stay in the hospital. Comparison of the number of recurrences according to the result of using a radio wave scalpel and the classical surgical method (for tumor-like formations - 12% and 24.2%, respectively, for benign tumors - 8.3% and 40%, for malignant tumors - 30% and 70%) indicates a high effectiveness of surgical treatment using "Surgitron".

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Article

The effect of simultaneous rhinoplasty and septoplasty on the development of postoperative pain syndrome

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Abstract: Introduction. One of the most difficult goals in facial reconstructive surgery is to eliminate defects in the external nose. Difficulties may arise with simultaneous septo- and rhinopalasty, as there is a need to restore and preserve the structures of the nasal cavity. To date, there are not many studies that would be aimed at assessing the pain syndrome after surgery on the structures of the nose, which was the impetus for studying this problem. The purpose of the study.

The purpose of this study was to study the severity of acute pain syndrome after septoplasty, rhinoplasty and rhinoseptoplasty.

Materials and methods. A total of 98 patients, 19 men and 79 women, aged from 18 to 45 years, were examined and operated on. The open rhinoplasty group (group 1) included 6 men and 27 women, the open rhinoseptoplasty group (group 2) – 7 men and 26 women, and the septoplasty group (group 3) included 6 men and 26 women. To ensure premedication, all patients were prescribed 2 ml of 0.4% dexamethasone solution, 4 ml of 0.2% ondacetron solution. Preoxygenation of 100% O2 5-6 l/min was carried out with the help of an anesthetic mask. Induction of anesthesia was carried out with 20 ml (200 mg) of 1% propofol emulsion. To achieve myoplegia, a solution of ridelate C (50 mg) was administered. For anesthesia purposes, 2 ml of 0.005% fentanyl solution (0.1 mg) was administered intravenously. Infiltration anesthesia during rhinoplasty was carried out using a 2% solution. Local anesthesia was performed by intramuscular administration of a 50 mg ketoprofen solution before surgery, 24 and 48 hours after manipulation, as well as for 3 days after it, taking into account the severity of the pain syndrome. After performing rhinoplasty, septoplasty and rhinoseptoplasty, the severity of the pain syndrome was assessed using a visual analog scale (VAS), a digital rating scale (DRS) and facial pain scale (FPS 3, 6, 24, 48 hours after the end of surgery.

Results. According to the VAS pain syndrome assessment, the pain intensity in group 1 was maximal one hour after rhinoplasty and subsequently had negative dynamics: on the 3rd, 6th ($p<0.001$), 24th ($p<0.05$) and 48th ($p<0.001$) hours after surgery. In groups 2 and 3, the highest pain intensity was recorded at the 3rd hour after surgery ($p<0.001$), compared with the hour after surgery. According to the DRS, the intensity of pain 3 hours after rhinoplasty in group 1 decreased, compared with his assessment 1 hour after surgery, and continued to decrease on the 3rd, 6th ($p<0.001$), 24th ($p<0.01$) and 48th hours ($p<0.001$). In group 2, 3 hours after surgical manipulation, the intensity of the pain syndrome increased significantly compared to the previous period of its assessment ($p<0.05$), which was also found in the group of patients after rhinoseptoplasty ($p<0.05$) at the same time. Assessing the severity of the pain syndrome according to FPS, in group 1, the pain syndrome was insignificant and did not cross the threshold. In patients of groups 2 and 3, compared with the 1st hour after the interventions, pain syndrome significantly increased after 3 hours ($p<0.001$), but subsequently decreased. Conclusion. Based on the analysis of acute postoperative pain syndrome, this study confirms that septoplasty is a more traumatic intervention compared to rhinoplasty, and surgical operations in

the area of the external nose and on the nasal septum in the early postoperative period entail excalation of stress reactions, relative to rhinoplasty and septoplasty.

Keywords: septoplasty, rhinoplasty, pain, trigeminal nerve.

1. Introduction

Elimination of defects of the external nose is one of the most difficult goals in reconstructive facial surgery, which is due to the connection of reconstructive and aesthetic tasks of plastic surgery [1, 2]. Simultaneous rhinoplasty and septoplasty complicate these tasks due to the need to restore and / or preserve the internal structures of the nasal cavity, for example, the thickness of the nasal septum in the case of autotransplantation cartilage, the structure of the external and internal nasal valves, etc. [3, 4]. Pain syndrome has not only medical, but also social significance [5]. Currently, there are very few studies aimed at assessing acute pain syndrome depending on the type of rhinosurgical intervention in the available literature, which determines the relevance of studying this issue.

2. Patients and Methods

2.1. Patients .

The study was conducted in the period from 2020 to 2023. 98 patients were examined and operated on, among them 19 men and 79 women aged 18 to 45 years. Group 1 (open rhinoplasty) consisted of 6 men and 27 women (n=33, 18-44 years), group 2 (open rhinoseptoplasty) – 7 men and 26 women (n=33, 20-43 years), and group 3 (septoplasty) – 6 men and 26 women (n=32, 21-45 years old).

2.2. Anesthesiological manual.

All patients received 2 ml of 0.4% dexamethasone solution and 4 ml of 0.2% ondacetron solution as premedication. Preoxygenation of 100% O2 5-6 l/min was carried out with the help of an anesthetic mask. Induction of anesthesia was carried out with 20 ml (200 mg) of 1% propofol emulsion. For the purpose of myoplegia, a solution of ridelate C (50 mg) was administered. For anesthesia purposes, 2 ml of 0.005% fentanyl solution (0.1 mg) was administered intravenously. After that, the trachea was intubated through the mouth with tubes No. 6.5-8. Artificial ventilation of the lungs was carried out by the Mindray Wato apparatus in the mode of forced normoventilation along the reverse circuit with the parameters of BPD 12 per minute, respiratory volume - 500.0 ml, minute respiratory volume – 6.0 l/min, EtCO2 32-35 mmHg, SaO2 99-100%. The basis of anesthesia: PSG (O2+air) 2 l/min, FiO2 0.5%+ sevoflurane 2.5 vol%, MAK 0.9%. Anesthesia was maintained using 6 ml of 0.005% fentanyl solution (0.3 mg). In addition, 500.0 ml of 0.9% sodium chloride solution, 1000.0 ml of Ringer's solution, tranexam 500.0 mg, vetorolac solution (60 mg) were administered intravenously.

2.3. Local anesthesia.

During rhinoplasty, infiltration anesthesia was performed with a 2% lidocaine solution in the area of the columella, in the vestibule of the nasal cavity, in the area of the septum, tip, wings, back and root of the nose and lateral slopes, as well as conducting anesthesia of the subglacial, suprablock and supraorbital nerves. Next, a marginal endonasal and inverted V-shaped transcolumellar incision was performed with the blade of scalpel No. 15c. Also, during the septoplasty, the mucosal cartilage sheet was hydro-separated with a 2% lidocaine solution.

2.4. Analgesic therapy with nonsteroidal anti-inflammatory drugs (NSAIDs).

Ketoprofen solution of 50 mg was administered intramuscularly to all patients as an analgesic before surgery, 24 and 48 hours after surgery and for 3 days after it, depending on the severity of the pain syndrome. Analgesic was used if the pain level on one of the analog pain scales was higher than 25 mm and corresponded to "moderate pain" on the facial pain scale (FPS) (Fig. 1) [6].

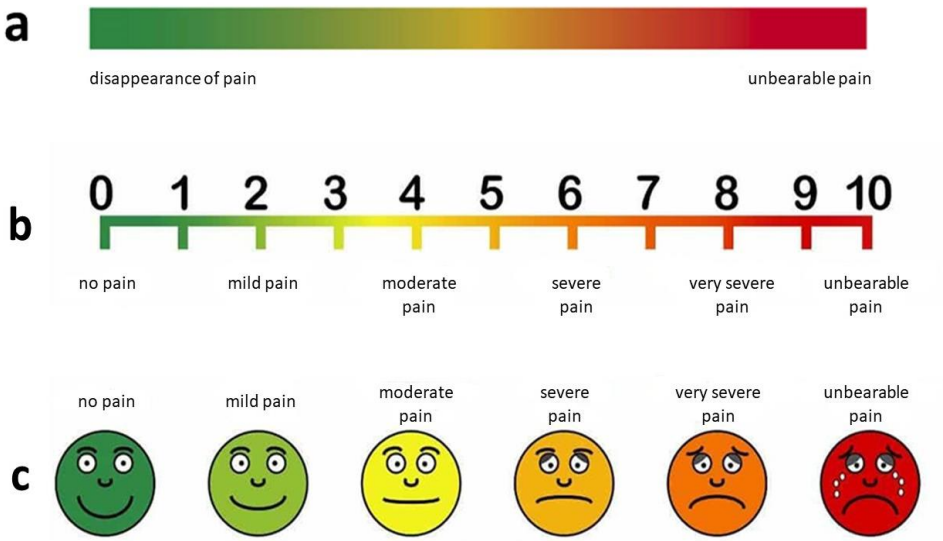

Figure 1. Analog scales of pain syndrome assessment after abdominoplasty and liposuction of the anterior abdominal wall. A – visual-analog scale, B – digital rating scale, C – facial pain scale.

2.5. Pain syndrome assessment.

Acute pain syndrome after rhinoplasty, rhinoseptoplasty and septoplasty was assessed using a visual analog scale (VAS), digital rating scale (DRS) and FPS 3, 6, 24, 48 hours after the end of surgery (Fig. 1). Patients were given color samples of scales before surgery and explained, how to use them during the assessment of pain syndrome. The survey of patients was conducted by researchers in a face-to-face format. Patients were shown scales in the following order and separately: VAS, DRS, FS. The digital value that corresponded to the pain experienced by the patient met the following criteria: 0 is the absence of pain, and 10 is unbearable, maximum possible pain. FPS was proposed to be used as follows: the faces were orally numbered in order from left to right, and the patient marked the face that corresponded to the severity of the pain. So, the first, green, face corresponded to the absence of pain, and the sixth, red, to the maximum, unbearable pain.

All patients gave written informational consent to surgical interventions and clinical research before performing surgical interventions. The study was approved by the Local Ethics Committee of the RUDN Medical Institute, Protocol No. 1 of 10/21/2021.

3. Results

3.1. Pain syndrome assessment by VAS.

According to the assessment of acute postoperative pain syndrome on a visual-analog scale, in the first group, the intensity of pain was maximal an hour after rhinoplasty and then had negative dynamics: on the 3rd, 6th ($p<0.001$), 24th ($p<0.05$) and 48th ($p<0.001$) hours after surgery. In the rhinoseptoplasty (group 2) and septoplasty (group 3) groups at the postoperative 3rd hour, according to the Mann-Whitney criterion, the significantly highest pain intensity ($p<0.001$) was recorded, compared with the hour after surgery. In group 2, pain initially and continued to decrease on the 6th ($p<0.001$), 24th ($p<0.01$) and 48th ($p<0.001$) hours after surgery (Fig. 1a, Table 1).

pain assessment time (hours)		1	3	6	24	48
1 group	VAS, мм	46,29±3,29	36,17±2,33	24,62±2,33	19,44±1,73	13,15±1,99
2 group		45,4±2,33	55,67±1,74	48,51±1,84	39,81±1,44	15,33±1,42
3 group		44,36±2,86	54,91±2,02	39,33±1,59	28,67±1,8	16,03±1,41
1 group	NRS, мм	49,59±2,41	37,3±2,13	23,26±2,52	17,87±1,83	10,1±1,33
2 group		50,1±2,62	57,99±2,33	46,72±2,53	37,77±1,95	11,15±1,44
3 group		47,33±2,33	55,212,33±	40,67±1,99	29,05±2,04	10,03±1,21
1 group	FPS, face number	2,62±0,2	2,56±0,25	1,2±0,11	1	1
2 group		2,73±0,24	3,61±0,15	2,76±0,16	1,89±0,18	1,2±0,3
3 group		2,71±0,3	3,77±0,1	2,53±0,14	1,46±0,09	1,13±0,7

Table 1. Average indicators of pain syndrome in the postoperative period.

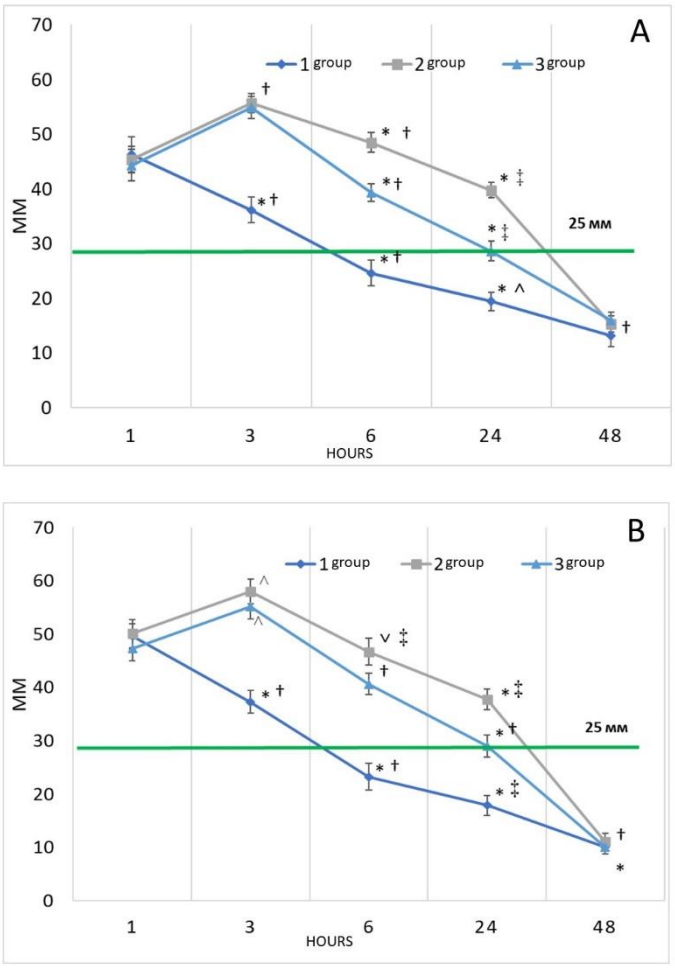

Figure 2. Dynamics of changes in pain syndrome in groups based on the results of its assessment using VAS (a), NRS (b) and FPS (c). Notes: † – significant differences between pain assessment periods ($p<0.001$); ‡ – significant differences between pain assessment periods ($p<0.01$); – significant differences between pain assessment periods ($p<0.05$); * – significant differences between groups after surgery ($p<0.001$); – significant differences between groups after surgery ($p<0.01$).

The same dynamics was recorded in group 3 as in group 2. According to the Mann-Whitney criterion, 3 hours after surgical interventions, patients of group 1 had a significantly lower level of pain syndrome than patients of groups 2 and 3 ($p<0.001$). After 6 hours, the pain syndrome in patients undergoing septoplasty was significantly higher than in patients after rhinoplasty and lower than in patients after rhinoseptoplasty ($p<0.001$) (Fig. 1a, Table 1). According to the Student's criterion, 24 hours after surgery, the pain in group 3 patients was higher than in group 1 patients ($p<0.01$), and the same as in group 3 patients ($p<0.001$). It should be noted that the pain syndrome at this time of its assessment was higher than the clinically significant indicator of 25 mm only in patients of the 2nd group. Two days after the surgical interventions, the patients experienced almost no pain.

3.2. Assessment of pain syndrome by DRS.

In the first three hours According to the Student's criterion, the intensity of pain syndrome according to DRS 3 hours after rhinoplasty in group 1 significantly decreased compared to its assessment 1 hour after surgery, and continued to decrease by the 3rd, 6th ($p<0.001$), 24th ($p<0.01$) and 48-th hours ($p<0.001$). In the septoplasty group, 3 hours after the end of surgery, the intensity of the pain syndrome significantly increased compared to the previous period of its assessment ($p<0.05$). The same was observed in the same period in the group of patients after rhinoseptoplasty ($p<0.05$) (Fig. 1b, Table 1). According to the Mann-Whitney criterion, in group 2, pain syndrome decreased at the 6th and 24th postoperative hours compared to the previous assessment points ($p<0.01$) and continued negative dynamics at the 48th hour after surgery ($p<0.001$). In the septoplasty group (group 3), the dynamics of the development of the intensity of pain syndrome, according to its assessment by DRS, was negative ($p<0.001$) (Fig. 1b, Table 1). An intergroup comparison of the pain syndrome according to the CRH showed that, according to the Student's criterion, 3 hours after surgery, the pain was stronger in patients who underwent septoplasty compared to those who underwent rhinoplasty ($p<0.001$), but lower than in those who underwent rhinoseptoplasty ($p<0.05$). According to the Mann-Whitney criterion, 6 hours after surgical interventions, the pain syndrome in patients of group 1 was significantly lower than in patients of the other groups ($p<0.001$). The intensity of pain in patients after rhinoseptoplasty was significantly higher than after septoplasty ($p<0.05$) (Fig. 1b, Table 1). According to the Mann-Whitney criterion, 24 hours after surgery, the intensity of pain after septoplasty was higher than after rhinoplasty, but lower than after rhinoseptoplasty ($p<0.001$) (Fig. 1b, Table 1). 48 hours after surgery, patients of all groups, according to the digital rating scale, did not experience pain syndrome and did not differ from each other.

3.3. Assessment of pain syndrome by FPS.

According to the assessment of the pain syndrome on the facial scale, in group 1, the pain syndrome was minimal and did not exceed the threshold corresponding to 25 mm conventional analog scales. Nevertheless, in the first three hours, patients from the first group felt minimal pain, which subsequently significantly decreased and was not clinically significant ($p<0.001$). In patients of the 2nd and 3rd groups, according to the Mann-Whitney criterion, in comparison with the 1st hour after surgical interventions, the pain syndrome significantly increased after 3 hours ($p<0.001$), and then significantly decreased, compared with the previous terms of its assessment ($p<0.001$) (Fig. 1b, Table 1). 3 and 6 hours after the end of operations, according to the Mann-Whitney criterion, pain syndrome had clinical significance and was significantly higher in groups 2 and 3, compared with group 1 ($p<0.001$). 24 hours after surgical interventions in group 3, the pain was significantly higher compared to group 1 ($p<0.001$), and lower compared to group 2 ($p<0.01$) (Fig. 1b, Table 1). 48 hours after surgery patients of all groups, according to the facial pain scale, did not experience pain syndrome and did not differ from each other.

4. Discussion

Rhinosurgery also causes psychological stress, in addition to stress caused by direct traumatization of tissues and the development of pain syndrome [3, 7, 8]. Psychological stress by itself can provoke cephalgia and, in combination with post–traumatic pain syndrome, its chronization [9, 10]. Ketoprofen, chosen by us as an NSAID, provides adequate analgesic therapy in the postoperative period [11-13]. [1, 2].

During rhinoplasty, acute pain syndrome is usually not pronounced, especially with high-quality postoperative analgesia [14-20]. In turn, septoplasty provokes the development of acute pain. So, as it was shown earlier by several authors, in conditions of inadequate analgesic therapy, inadequate anesthetic aid, it causes a powerful stress response, manifested both by changes in a number of physiological indicators and the development of pain in the first 3-6 hours [3, 8, 9, 21]. In this study, it was found that patients on all pain scales showed the most severe pain in the rhinoseptoplasty group in the first hours after surgery, which is consistent with the literature data [22, 23]. The difference between the rhinoplasty and septoplasty groups can be explained by the

difference in the innervation of the external nose and the nasal cavity. Thus, the nasal cavity receives a special vegetative innervation, which ensures the development of stress reactions of the body after septoplasty, which has been shown in clinical and experimental studies [8, 24-32]. So, sympathetic nerve fibers depart from T1-T3, form a synapse in the upper cervical ganglia, then pass through the internal carotid plexus and finally join the deep stony nerve and the nerve of the pterygoid canal. The wedge-palatine ganglion in the pterygoid canal also contains sympathetic fibers going to the nose and paranasal sinuses [33].

After rhinosurgical interventions, the severity of pain largely depends on the invasiveness of the operation itself. In most patients, there is a tendency to severe pain for the first time hours after surgery, followed by its decrease over time [30, 34]. The combination of the greatest invasiveness in group 2, compared with the first and third groups, can explain the severity of acute pain syndrome in the postoperative period.

5. Conclusions

Based on the analysis of acute postoperative pain syndrome, this study confirms the fact that septoplasty is a more traumatic surgical intervention compared to rhinoplasty, and the combination of surgery in the area of the external nose and on the nasal septum in the early postoperative period provokes an increase in stress reactions (an increase in the concentration of cortisol in blood plasma, an increase in the intensity of pain syndrome), according to compared with septo- and rhinoplasty.

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Article

Effect of antioxidant dental gel on the adaptation of the oral mucosa to removable dentures.

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Abstract: Determination of the effect of a gel with natural astaxanthin on the timing of adaptation of the oral mucosa to removable dentures. The gel made from a natural antioxidant reduces the risk of stomatitis, values of hygienic indices and traumatic factor. *Aims*: Reduction of the period of adaptation to removable dentures in patients with partial adentia. The objective was to evaluate the effect of antioxidant gel on the oral mucosa. *Patients and Methods*. The state of oropharyngeal microbiocenosis was studied in 105 patients aged 30-65 years old who were divided into three groups: the main group - 45 patients; comparison group - 35 patients; control group - 25 patients. The groups were comparable by age; gender differences were not taken into account. Patients in the main group received astaxanthin gel for 7 days after the delivery of the removable denture. Patients in the comparison group did not receive astaxanthin gel after the delivery of the removable denture. Clinical indices were used to assess oral hygiene: oral hygiene index plaque index API, gingivitis index, papillary-marginal-alveolar - (PMA); gingival sulcus bleeding index – SBI. We used a therapeutic and prophylactic agent in the form of a gel containing natural astaxanthin - 0.026%, vitamin E - 2.2%, Coenzyme Q - 1.5%. *Result*. According to the results of the analysis of the visual control and the results of photometric registration of the speed of healing and adaptation of the patient to the prosthesis, the data obtained differed in the patients of the 1st and 2nd groups. Visual control data of the dynamics of inflammatory changes in the oral mucosa development, received by the results of semi-quantitative evaluation of the severity of edema and hyperemia indicate significant differences in the rate of their reduction depending on the type of the applied tactics. In the case of group 1, prophylactic gel was applied from the time of denture fitting, and in group 2, only denture correction was performed. Thus, the index of hyperemia intensity testified to the dis-appearance of signs of the latter in Group 1 (gel with natural astaxanthin) - by the 4th day of observation, in Group 2 - by the 10th day after prosthesis correction. Complete disappearance of the signs of edema, respectively, was ascertained: in Group 1 - on the 4-5th day of observation and in Group 2 - by the 10th-11th day, at that, edema was retained 1-2 days longer. The method of photoplanimetric registration of the healing rate objectively confirmed the results obtained. *Conclusion*. Studies of the effectiveness of the gel containing natural astaxanthin indicate improved oral hygiene parameters of patients and reduced concentration of bacterial endotoxin and plasmalogen metabolites of oral microorganisms after 7 days of using the gel. Prophylactic dental gel with astaxanthin reduces the rate of adaptation to removable dentures by 1.7 - 2 times and reduces the risk of denture stomatitis due to wound healing, anti-inflammatory and anti-microbial action.

Keywords: natural astaxanthin, partially removable denture, hyperemia, anti-inflammatory effect, antioxidant.

1. Introduction

The purpose of this clinical study: to determine the terms of adaptation of oral mucosa to removable dentures on the normalization of basic hygienic and biochemical indicators when using the therapeutic and prophylactic agent in the form of a gel with natural astaxanthin. The task was set: to evaluate the effectiveness of antioxidant gel application in patients with partial secondary adentia.

Protection against oxidation and cell destruction in the body belongs to antioxidants. However, under certain conditions almost all of them turn into pro-oxidants and begin to harm the body by increasing the oxidation process. Inside the body, free radicals harm tissues and the immune system by destroying cells and DNA structure [1]. Universal adaptogens include antioxidants, so they are used in the treatment and prevention of diseases of the oral mucosa [2, 3].

Natural astaxanthin, due to the peculiarity of its biochemical structure, is the most powerful antioxidant that does not turn into a pro-oxidant [4, 5, 6]. It has prolonged anti-inflammatory and immunomodulatory effects. Its positive use in the treatment of cardiovascular diseases and cancer is known [7, 8].

The oral mucosa has good protective and barrier functions in response to the various mechanical and traumatic lesions to which it is exposed. However, when exposed to mechanical traumatic lesions of greater force, some changes occur [9]. The response to various stimuli in the oral mucosa depends on the nature, strength, duration and duration of the provocative factor. When exposed to any traumatic agent there is a response in the form of inflammation [10, 11, 12].

Traumactic denture stomatitis is common in dental practice. The complaints of patients with denture stomatitis are pain in the area of the denture bed at the site of injury, which increases when using dentures [1, 2]. The causes of this pathology may include poor workmanship, the presence of roughness of the denture. Single roughnesses and pores in the base of a removable denture can also cause focal inflammatory processes in the oral mucosa. A limited catarrhal inflammation of the oral mucosa occurs if the denture is used for a short period of time. If the traumatic factor is not eliminated, swelling and hyperemia will occur, which may lead to the subsequent formation of erosions. With prolonged exposure to the traumatic factor, ulcers can develop on the oral mucosa. The key to the successful treatment of traumatic denture stomatitis is the timely correction of the dentures and the absence of signs of inflammatory diseases of the oral mucosa [7, 13].

Modern medicine focuses on preventive measures aimed at regulating the balance of the oral microflora, and stimulating natural protective mechanisms to eliminate pathogenic agents [1]. So in the majority of therapeutic and prophylactic means for oral care, manufacturers already include antiseptics of a wide spectrum of action: triclosan, chlorhexidine and others. These components are included in most hygiene products of different forms of use: toothpaste, gels, balms and rinses [14, 15, 16]. Given the advertising and promotional activities on television and radio broadcasts, these products are among those widely used and dominate among the rest. However, it should be taken into account that despite the success of the above antiseptics in the correction of oral microbiocenosis, the literature data also indicate their adverse effect on the composition of oral fluid microbiota [17].

It was found that natural astaxanthin contributes to the regulation of oral microbiocenosis, having anti-inflammatory, antimicrobial, wound-healing effect [18]. On the basis of this natural antioxidant was made dental gel to reduce the period of adaptation to removable dentures, as well as the prevention of denture stomatitis oral cavity. The action of astaxanthin is enhanced by vitamin E and coenzyme Q [12].

2. Aims

Reduction of the period of adaptation to removable dentures in patients with partial adentia. The objective was to evaluate the effect of antioxidant gel on the oral mucosa.

3. Materials and methods

The state of oropharyngeal microbiocenosis was studied in 105 patients aged 30-65 years old who were divided into three groups: the main group - 45 patients; comparison group - 35 patients; control group - 25 patients. The groups were comparable by age; gender differences were not taken into account. Patients in the main group received astaxanthin gel for 7 days after the delivery of the removable denture. Patients in the comparison group did not receive astaxanthin gel after the delivery of the removable denture. The inclusion criteria for the control group were patients with

one or two metal-free crowns, no removable dentures, no signs of periodontal and oral mucosal inflammation, and no dental anomalies or deformities. Patients with cancer, immunodeficiency diseases, diabetes mellitus and severe somatic condition, as well as smokers and pregnant women were excluded from the study.

Clinical indices were used to assess oral hygiene: oral hygiene index plaque index API, gingivitis index, papillary-marginal-alveolar - (PMA); gingival sulcus bleeding index - SBI [3]. The calculation was performed according to the methods of index calculation by the authors of the indices [1].

The state of oropharyngeal microbiocenosis was assessed according to the concentrations of bacterial plasmalogens and endotoxin determined by gas chromatography mass spectrometry of saliva [13].

We used a therapeutic and prophylactic agent in the form of a gel containing natural astaxanthin - 0.026%, vitamin E - 2.2%, Coenzyme Q - 1.5% (RF patent No 2599026 "Composition for healing tissues in the oral cavity" Bulletin No 28 of 8.09.2016 Declaration of compliance, main registration number: 1037739230979. Oral hygiene product "Astadent", compliance with TU 20.42.18-001-28910991-2017).

Examination of the patients' oral cavity, as well as oral fluid analyses to determine the concentrations of small molecules by gas chromatography mass spectrometry were taken at 3 stages of the study: Stage 1 - before gel application, Stage 2 - after 7 days of gel exposure, Stage 3 - after 28 days of gel application.

The evaluation of clinical manifestations in the oral cavity in patients of the main group (group 1) and group 2 after the application of partial dentures in the oral cavity was carried out.

The 45 patients of group 1 (21 female, 24 male, 25 imediate dentures and 20 removable partial dentures), who received the gel within 7 days from the first day of placing the removable denture, had hyperemia of the denture bed in 86.6% of cases and edema in 55.6% of patients with imediate dentures, erosions were not observed. The 20 patients with partial dentures showed hyperemia in 70% of cases and edema in 25% of cases, no erosions were observed.

Oral pigmentary state was also studied using API, PMA and SBI indices in group 1-3 patients on days 1, 7, 28 of the study and concentrations of bacterial plasmalogens and bacterial endotoxin were studied by gas chromatography and mass spectrometry.

The incidence of morphological types of complications in 35 patients in group 2 during the primary application of removable prosthesis directly due to the irritating mechanical impact on the oral mucosa was in 17 patients with imediate prosthesis (100% cases) and in the majority of patients with plate prosthesis (94,4% of cases). At the same time, hyperemia and edema were also more pronounced and erosions were more frequent in patients with immediate prostheses. Erosions occurred in 71.4% of cases.

At each examination, a visual assessment of the state of the oral mucosa and prosthetic bed tissues was performed, and if indicated, the design was corrected. The intensity of inflammation in the erosion or ulcer zone was assessed according to two parameters: the degree of swelling and hyperemia.

We used a semi-quantitative method to assess a particular manifestation, which consisted in assigning one of 5 conditional ranks (points) to each degree of the observed changes: 0, no corresponding change; 1.0, weak degree of its manifestation; 2.0, moderate degree; 3.0, strong degree; and 4.0, very strong degree. The evaluation was made before the beginning of the prosthesis and at time points: 2, 4, 6, 8, and 10 days. The data obtained in each selected group were averaged, and the mean values obtained were used in further statistical analysis.

Photo-planimetric control of hyperemia reduction was determined by taking photographs of the prosthetic bed at their standard magnification. A point planimetric grid of 49 points was superimposed on the photographs. By counting the number of points per wound surface and comparing this index with the previous result, the percentage of the healing rate of the oral mucosa in the dynamics was determined. Photographs were taken with a digital camera Nicon D60, lens - sigma 24 -70 mm f2.8 EX DG Macro with the subsequent grid overlay in the Photoshop CC photo editor before the placement of the removable prosthesis and at the time of: 2, 4, 6, 8 and 10 days.

4.Research results and their discussion

A positive prophylactic and anti-inflammatory effect of astaxanthin gel was established in patients with imediated and partial removable dentures. Application of the gel in the short term at the stage of 7 days contributes to a decrease in the values of hygiene indices, concentrations of bacterial plasmalogen and endotoxin in the oral fluid.

According to the results of the analysis of the visual control and the results of photometric registration of the speed of healing and adaptation of the patient to the prosthesis, the data obtained differed in the patients of the 1st and 2nd groups. Visual control data of the dynamics of inflammatory changes in the oral mucosa development, received by the results of semi-quantitative evaluation of the severity of edema and hyperemia indicate significant differences in the rate of

their reduction depending on the type of the applied tactics. In the case of group 1, prophylactic gel was applied from the time of denture fitting, and in group 2, only denture correction was performed. Thus, the index of hyperemia intensity testified to the disappearance of signs of the latter in Group 1 (gel with natural astaxanthin) - by the 4th day of observation, in Group 2 - by the 10th day after prosthesis correction. Complete disappearance of the signs of edema, respectively, was ascertained: in Group 1 - on the 4-5th day of observation and in Group 2 - by the 10th-11th day, at that, edema was retained 1-2 days longer. The method of photoplanimetric registration of the healing rate objectively confirmed the results obtained.

In addition, the evaluation of clinical manifestations in the oral cavity of the patients of the main group (group 1) and group 2 after the application of partial dentures in the oral cavity was carried out. Comparative data are presented in Table 1.

Table 1. Prevalence of clinical manifestations in the prosthetic bed area after the delivery of a partial denturenge. * - reliability P≤ 0.05.

Symptoms	Group 1 (n=45)	Group 2 (n=35)
Hyperemia	39 (86,6%)	35 (100%)
Swelling	25 (55,6%)	34 (97,1%)
Erosion	0	25 (71,4%)

According to the data shown in Table 1, we can conclude that the clinical manifestations and complaints in the oral cavity of patients in Group 1 with the use of prophylactic gel based on natural astaxanthin, which proves the preventive effect of dental gel and the lack of need for correction of dentures. Patients in Group 2 required correction in the first week after placing removable dentures.

The evaluation of the effectiveness of the gel in terms of changes in the hygienic state of the oral cavity is presented in Fig. 1,2,3. Figure 1 shows the average values of API index for 1,2 and group 3 (G.C.) and at 3 stages of the study: before gel application, 7, 28 days after gel application.

Table 2. API index in patients at different stages of the study.

API Index, %	Averages		
Duration, day	Core group	Comparison group	Control group
0	77,5	78,5	48
7	65	88	51
28	59	77	49

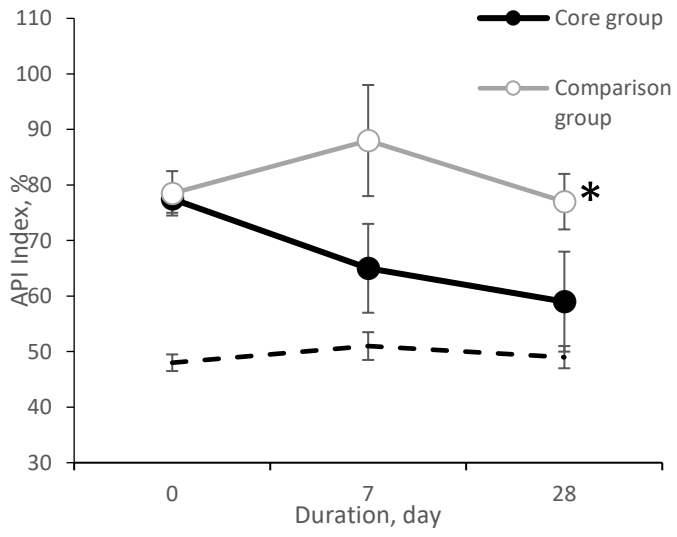

Figure 1. API index in patients at different stages of the study. * - significant difference in the group relative to the 1st stage of the study, p<0.05.

Figure 1 shows that in the main group there is a value of the API index exceeding the value of 70% - the boundary of unsatisfactory state of the mouth at the initial stage before treatment and reliably exceeding the average values of the indices in comparison group patients. In 7 and 28 days after using the gel a tendency to a decrease of API index values to the area of values characterizing satisfactory state of the mouth cavity was observed in the patients of the main group. Group 2 patients' API did not change significantly. Thus, the positive influence of the gel on the hygienic state of the mouth cavity in the part of the dental plaque is noted.

Changes in the index of oral gingivitis in patients before and after using the gel is shown in Fig. 2.

Table 3. PMA index in patients at all stages of research.

PMA Index, %	**Averages**		
Duration, day	Core group	Comparison group	Control group
0	38,5	42	9
7	35	55	8
28	31,5	50	10

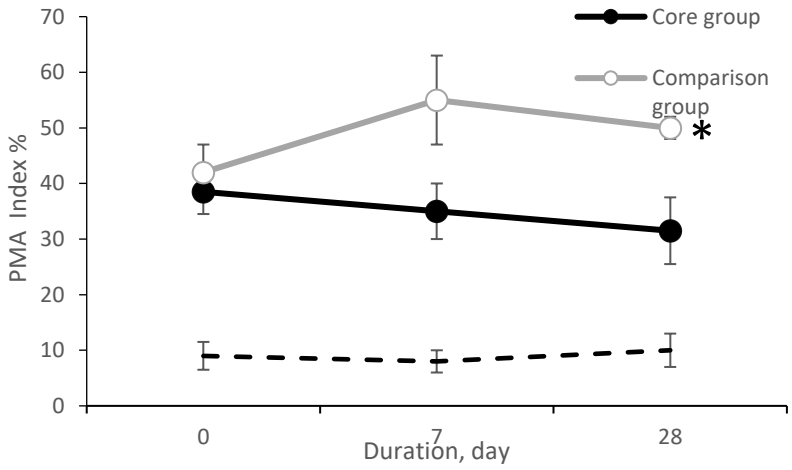

Figure 2. PMA index in patients at different stages of the study. * - reliable difference in the group in comparison with the 1st stage of the study, p<0,05.

There was a PMA index value characterizing unsatisfactory periodontal condition (40-60%) in Group 1 and 2 patients before the study. The PMA index values in all groups increased in groups 1 and 2, compared to group 3. As a result of using the gel, there was a tendency for the index to decrease on days 7 and 28 in the main group. In group 2, the PMA index values did not change significantly.

The follow-up results in group 1 compare the PMA values with those in group 3 and have a reliable difference with the initial value in their group.

Changes in the SBI hygiene index (gingival sulcus bleeding) in patients of the main groups and comparison group (GC) before and after the use of the gel are shown in Figure 3.

Table 4. SBI index in patients at all stages of the study.

SBI Index, %	**Averages**		
Duration, day	Core group	Comparison group	Control group
0	2	2	0
7	1	2,5	0

28	0,5	2	0
Scatter			
0	0,9	0,5	0
7	0,8	0,5	0
28	0,5	0,4	0

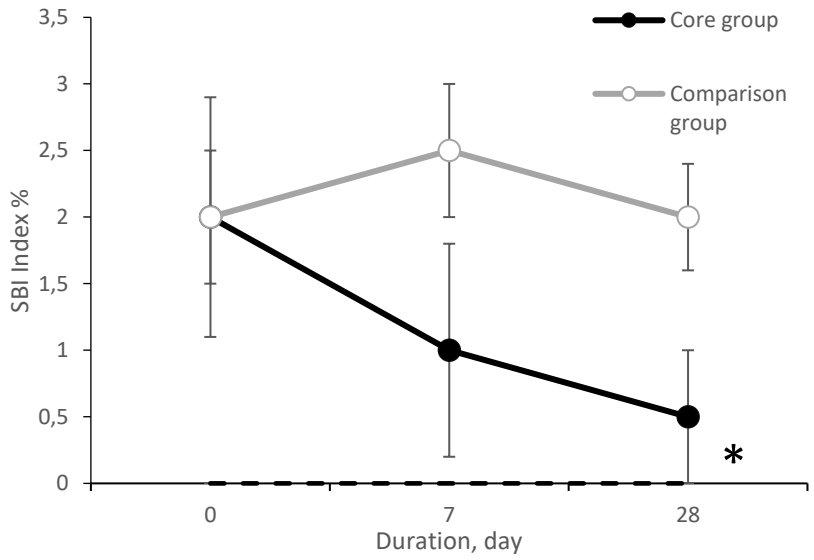

Figure 3. Bleeding index in patients at different stages of the study. ***** - a significant difference in the group relative to the 1st stage of the study, p<0,05

In the 1 (main) group SBI index values had a significant difference from the 2 and 3 groups. In the main group there was a tendency to reduce the SBI values after the application of the gel. Thus, the obtained data indicate the absence of bleeding during probing.

Changes of plasmalogen and endotoxin concentrations by gas chromatography mass spectrometry in the oral liquid of the patients of the 1st (main) group and comparison group are shown in Figures 4 and 5.

Table 5. The concentration of bacterial plasmalogen in patients at all stages of the study.

Plasmalogen, mg/ml	**Averages**		
Duration, day	Core group	Comparison group	Control group
0	5,64	5,2	0,83
7	0,22	6,2	0,92
28	0,21	5,5	0,88
Scatter			
0	2	2	0,5
7	0,2	2,2	0,5
28	0,15	2,4	0,5

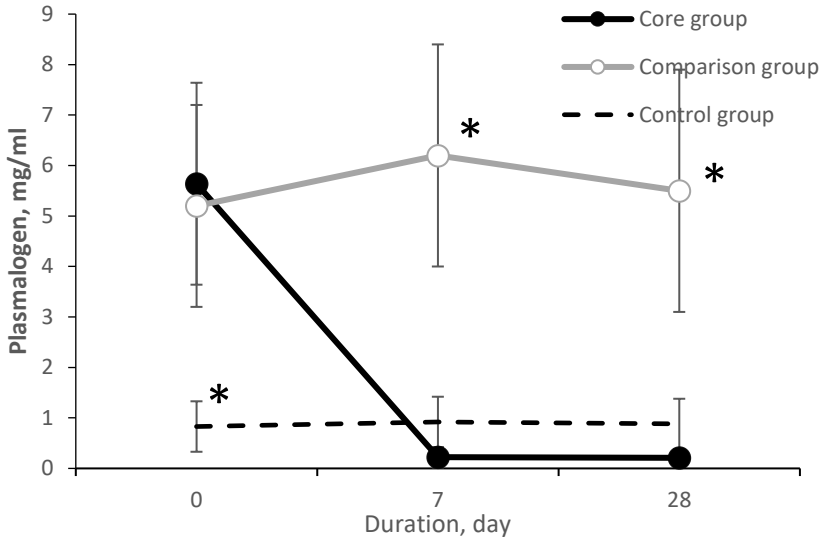

Figure 4. Concentration of bacterial plasmalogen in oral fluid in patients of groups 1, 2 and 3.* - significant difference in the group relative to the 1st stage of the study, p<0.05.

Table 6. The concentration of bacterial endotoxin in patients at all stages of the study.

Endotoxin, nanomole/ml	**Averages**		
Duration, day	Core group	Comparison group	Control group
0	3,56	3,5	0,48
7	0,79	3,9	0,52
28	1,01	3,8	0,55
Scatter			
0	1	0,6	0,2
7	0,5	0,8	0,15
28	0,5	0,5	0,2

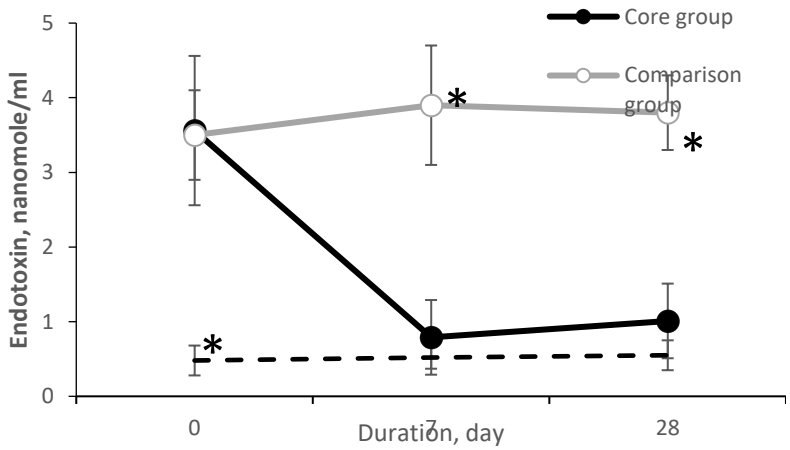

Figure 5. Concentration of bacterial endotoxin in oral fluid in patients of groups 1, 2 and 3.* - significant difference in the group relative to the 1st stage of the study, p<0.05.

The graphs in Figure 4 show that the concentration of bacterial plasmalogen in the oral fluid of patients in groups 1 and 2 is increased relative to normal (50mcg/ml). In group 1, the concentration of bacterial plasmalogen in the oral fluid decreases and remains low on days 7, 28. The decrease

in the concentration of bacterial plasmalogen in the oral fluid immediately after the start of the gel can be explained by the antiseptic action of the gel component - astaxanthin. In group 2 the concentration of bacterial plasmalogen does not change statistically.

As a result of using the gel, the activity of the oral microflora decreases, which leads to a decrease in the concentration of plasmalogen in the oral fluid, with a constant concentration of plasmalogen in the blood. Similar trends in the concentration of bacterial endotoxin in the oral fluid can be noted after 7 days in patients 1 (main) group in the graphs shown in Fig. 5.

Changes in the concentration of bacterial endotoxin in the oral fluid are also explained by the local antiseptic action of astaxanthin. The tendency to a decrease in the concentration of bacterial endotoxin in oral fluid is an indirect indication of a decrease in the intensity of microbial infestation of the oral cavity, indicating a positive anti-inflammatory effect of natural astaxanthin.

The findings of the study are consistent with the literature on the mechanism of action and antimicrobial properties of natural astaxanthin. The mediated anti-inflammatory mechanism of action is the inhibition of cyclooxygenase 1 enzyme, neutralization of free radicals in mitochondria, suppression of inflammatory mediators such as: Tumor necrosis factor, Prostaglandin, interleukins, etc. [16-18].

5. Conclusion

Prophylactic dental gel with astaxanthin reduces the rate of adaptation to removable dentures by 1.7 - 2 times and reduces the risk of denture stomatitis due to wound healing, anti-inflammatory and antimicrobial action.

Thus, the study confirmed the positive prophylactic and anti-inflammatory effects of astaxanthin gel in patients with imediated and partial removable dentures. The application of the gel in the short-term at the stage of 7 days contributes to the reduction of values of hygiene indices, concentrations of bacterial plasmalogen and endotoxin in the oral fluid of group 1 patients. Index of hyperemia intensity, testified to the disappearance of inflammation signs in Group 1 (gel with natural astaxanthin) - by the 4th day of observation, in Group 2 - by the 10th day after denture correction. Complete disappearance of the signs of edema, respectively, was found: in Group 1 - on the 4-7th day of observation and in Group 2 - by the 10th-11th day, moreover, edema retained for 3-5 days longer. The method of photoplanimetric registration of the healing rate objectively confirmed the results obtained.

Studies of the effectiveness of the gel containing natural astaxanthin indicate improved oral hygiene parameters of patients and reduced concentration of bacterial endotoxin and plasmalogen metabolites of oral microorganisms after 7 days of using the gel. Prophylactic dental gel with astaxanthin reduces the rate of adaptation to removable dentures by 1.7 - 2 times and reduces the risk of denture stomatitis due to wound healing, anti-inflammatory and antimicrobial action.

Conflicts of Interest: The authors declare no conflict of interest

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Article

Creation of an antioxidant gel for the prevention of viral diseases of the oral mucosa.

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Abstract: This article examines the effects of an antioxidant gel with astaxanthin on the elements of damage to the oral mucosa caused by the herpes simplex virus. The anti-inflammatory, immunomodulatory and wound-healing effects of this drug have been noted.

Keywords: astaxanthin, herpetic stomatitis, gel, ingredients, composition

1. Introduction

Viral diseases of the oral mucous membrane is one of the most important problems in dentistry. Acute herpetic stomatitis occupies a special place in this problem, primarily because this stomatitis accounts for more than 80% of all oral mucosal diseases in children [1,3,4,5]. In addition, acute herpetic stomatitis occupies one of the leading places in the pathology of the oral mucosa, occurring more frequently than scarlet fever, measles, and only slightly inferior to chicken pox.

Recently, scientists of different specialties have come to the conclusion that the basis of many pathological processes in the body, in particular the oral cavity, leading to various diseases, is the same phenomenon. It is the damage of cell membranes and other structures inside the cell by free oxygen radicals. Depending on which structures are damaged: - The hereditary substance (DNA) or the outer membrane, either cancer develops or other disorders are observed[3]. As the body ages, free radical activity increases and the risk of various age-related diseases increases. Now that the cause of these negative changes is known, many medical centers are developing substances that can counteract the effects of free radicals. Free-radical oxidation (FRO) processes are constantly going on in cells and are necessary for the body to carry out a number of important functions, including respiration. However, in a healthy body, free-radical oxidation (FRO) processes are under the control of the antioxidant defense system (AOD), which includes an enzymatic system (superoxide dismutate, glutathione peroxidase, catalase) and bioantioxidants [2,6,7].

Herpes simplex virus is a genus of the alphaherpesvirus subfamily. It is neurotropic and neuroinvasive, which means that the virus cells migrate into the nervous system. This peculiarity allows it to establish itself in the host for the rest of its life after primary infection [1,5]. Viruses are intracellular infectious agents. Viral diseases affect cells that are already impaired, which the pathogen takes advantage of. Modern studies have proven that this only occurs when the immune system is severely weakened and is no longer able to deal with the threat at the proper level [2,6,8]. A huge role with regard to the protective function and the fight against infectious agents belongs to antioxidants. The strongest of them is natural astaxanthin [3,7].

In our study, we decided to create an antioxidant gel based on natural astaxanthin and test its effect on the lesion elements in acute herpetic stomatitis.

2. Materials and methods:

Included the development and technology of obtaining dental gel based on natural astaxanthin. In full accordance with the requirements of the State Pharmacopoeia of the Russian Federation XIII in the manufacture of prophylactic gel for the standardization of the dosage form was carried out to develop a method of quantitative determination of astaxanthin [8].

Astaxanthin is a carotenoid and belongs to the xanthophylls. The chemical name is (6S)-6-hydroxy-3-[(1E, 3E, 5E ,7E, 9E, 11E, 13E, 15E, 17E)-18-[(4S)-4- hydroxy-2,6,6-trimethyl-3- oxo-1-cyclohexenyl]-3,7,12,16- tetramethyloctadeca-1, 3, 5, 7, 9, 11, 13, 15, 17- nonaenil]-2,4,4- trimethyl -1-trimethyl-1-cyclohexa-2-yenon. The chemical formula is C40H52O4. In Fig. 1. the structural formula of astaxanthin is presented [8].

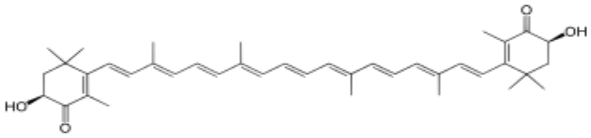

Figure 1: Structural formula of astaxanthin

We used astaxanthin obtained biotechnologically from the yeast Xanthophyllomyces dendrorhous. Astaxanthin was an oily liquid of bright orange color that mixes well with the hydrogel base to form a homogeneous microemulsion. Vitamin E and coenzyme Q were chosen as the main components of the prophylactic gel as gas pedals and synergists of astaxanthin.

To create a soft dosage form with asta xanthin in the form of a gel, the excipients presented un Table 1 were used.

Table 1. Composition of a soft drug formulation with astaxanthin

Component	**ND**	**Component assignment**
Carbopol	Eur.Ph.	Structure maker
Purified water	FS 42-2619-97	Solvent, the main component of the gel base dispersion medium
Triethanolamine pure	ThU 6-09-2448-86	Neutralizing agent
Nipazole	FS 42-2079-91	Conservative
Nipagin	FS 42-1460-89	Conservative

For the standardization of the gel dosage form, we carried out work to develop a method for the quantitative determination of astaxanthin, in full compliance with the requirements of State Pharmacopoeia of the Russian Federation XIII.

Carbopol, a sparsely crosslinked acrylic polymer with suitable technological characteristics, was used as structure-forming components. Gels based on sparsely crosslinked acrylic polymers are widely used in pharmacy as bases for soft dosage forms. They are white flaky hygroscopic powders of weakly acidic reaction, swelling in water and other polar solvents after d ispersion, which form stable gels after neutralization with solutions of basic substances [8].

Nipagin and nipazole were selected as preservatives in the soft dosage form. Nipagin (FS 42-1460-89) is a methyl ester of para-hydroxybenzoic acid. The propyl ester of parahydroxybenzoic acid is known as nipazole (FS 42-2079-91). Nipagin and nipazole are white crystalline powders,

hardly soluble in water, soluble in oils and easily soluble in organic solvents. Nipagin has the best solubility, so it is more often used in aqueous solutions.

Purified water (FS 42-2619-97) is a colorless transparent liquid without taste or smell, used as a solvent.

The composition of the gel (N 2599026 RF MPK7A61Q11/00 "Composition for healing oral tissues") is presented in Table 2.

Table 2. Composition of dental gel based on natural astaxanthin

Name of raw material	Quantity, g
Astaxanthin	0,13-0,26
Carbopol	1,0
Triethanolamine	1,0
Propylene glycol	1,5
Nipagin	0,1
Nipazole	0,05
Purified water	until 100,0

The proposed composition differs from the analogues in the simplicity of production. The dental gel is prepared on the basis of natural astaxanthin, which is the most powerful natural antioxidant with strong anti-inflammatory, immunomodulatory and wound-healing effects. The gel is applied both by the doctor and the patient himself into the oral cavity on the elements of lesions in the mouth.

Instrumental analysis of astaxanthin substance and finished dosage form in the form of gel was performed using the following equipment: Cary 50 UV/Vis spectrophotometer, JEOLJNMECA 600 NMR spectrometer (Japan), with a working frequency for 1H nuclei of 600 MHz. Mass spectra were recorded on an Agilent 6430 (QQQ) triple quadrupole mass spectrometer equipped with an ion source with chemical ionization at atmospheric pressure. Development of a method for quantitative determination of astaxanthin was performed using an Agilent 1290 high-performance liquid chromatograph equipped with a diode array detector.

All reagents and solvents used for qualitative and quantitative analysis were used.

The composition is prepared as follows. Preservatives (methyl and propyl esters of 4-hydroxybenzoic acid ester) are dissolved in propylene glycol. Then the carbopol gel is prepared. Small portions of carbopol are added to water, left to swell for 2-4 hours, then triethanolamine is added while stirring A solution of preservatives is added to the carbopol gel while stirring, then the active ingredients are stirred until a homogeneous gel is obtained, including astaxanthin. Vitamin E and coenzyme Q serve as gas pedals of natural astaxanthin in the dental gel [8].

For the purposes of standardization, the use of the finished dosage form in the form of a gel seems convenient because there is no need to introduce conversion factors and allows obtaining an integral value of the quantitative content of astaxanthin when using HPLC method for its analysis [8].

Antioxidant gel with astaxanthin was given to the patient. It was applied to the mucous membrane in the area of the secondary lesion element in acute herpetic stomatitis. The patient applied the obtained gel independently, 2 times a day. It was recommended to use the preparation for 5 days. The result of the study was noticed after two days of use.

Results

The resulting invention No. 2599026 Bulletin No. 28 of 08.09.2016 belongs to medicine, namely to dentistry and can be used for the prevention and treatment of viral diseases of the mucous membranes of the mouth and lips.

The technical result of the invention is the creation of a new composition that allows to increase the effectiveness of prevention and treatment of patients with viral diseases of the oral mucosa, due to the ease of use and improvement of local immunity, without causing allergic reactions and side effects [8].

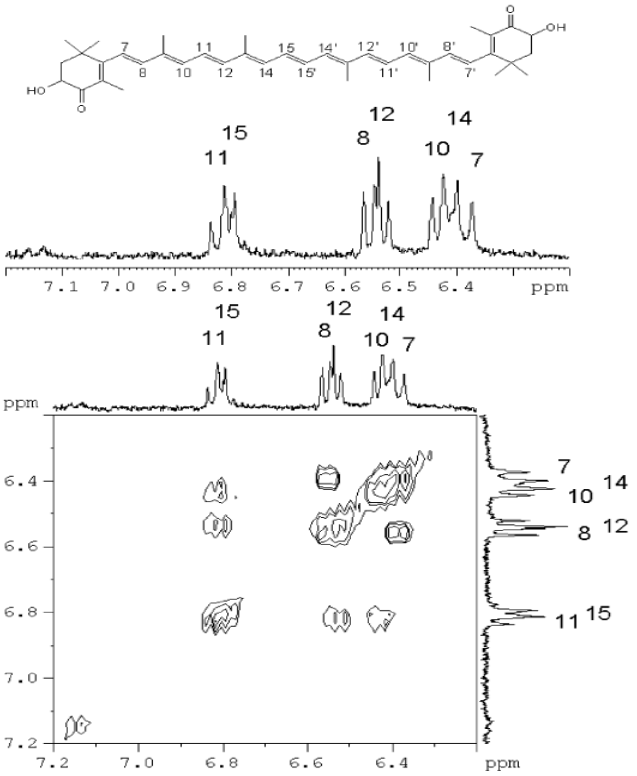

Figure 2. 1H nuclear magnetic resonance spectrum (A) and two-dimensional COSY nuclear magnetic resonance spectrum of trans-astaxanthin

The technical result is achieved by the fact that the composition for healing oral tissues contains in wt%:

Table 3: Composition of Astaxanthin Dental Gel

astaxanthin	0,12-0,26
vitamin E	1,4-2,2
coenzyme Q	0,8-1,5
propylene glycol	0,4-0,7
methyl ester of 4-hydroxybenzoic acid	0,07-0,12
propyl ester of 4-hydroxybenzoic acid	0,02-0,05
carbopol	0,4-0,7
triethanolamine	0,5-0,8
purified water	the rest

The proposed composition differs from the analogues in the simplicity of production. The dental gel is prepared on the basis of natural astaxanthin, which is the most powerful natural antioxidant with strong anti-inflammatory, immunomodulatory and wound-healing effects. The gel is applied both by the doctor and the patient himself into the oral cavity on the elements of lesions in the mouth. The composition of the gel does not cause unpleasant sensations - neither mechanical nor gustatory [8].

3. Conclusion:

The prepared antioxidant gel with astaxanthin has a powerful antioxidant, wound healing effect.

The developed gel belongs to the innovative development, as innovation is an implemented innovation that provides a qualitative increase in the efficiency of processes or products, demanded by the market.

Conflicts of Interest: The authors declare no conflict of interest

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