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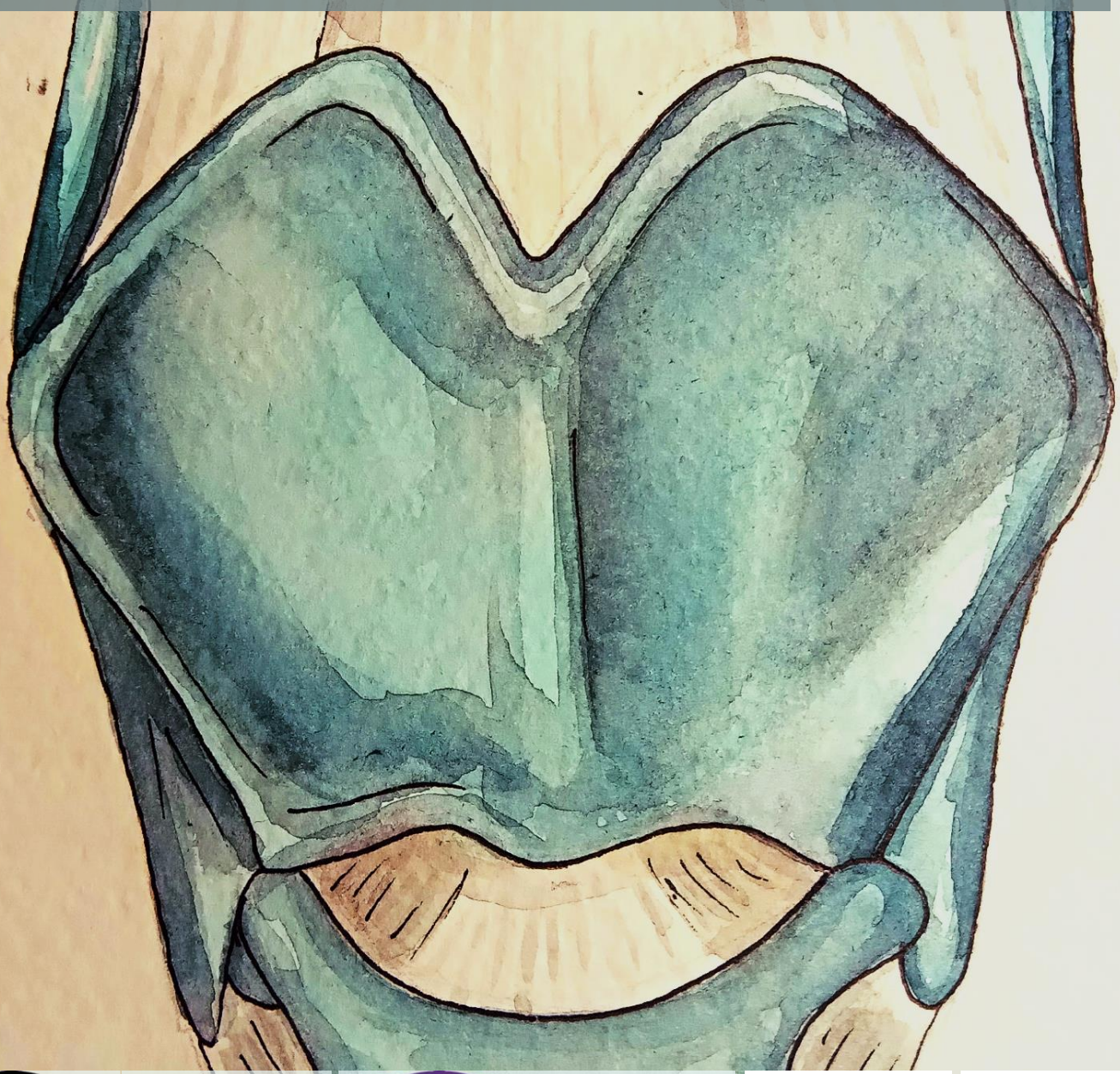

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Contents

The Journal OTORHINOLARYNGOLOGY, HEAD and NECK PATHOLOGY (ORLHNP) is a peer-reviewed medical and biological journal. Journal papers are published in English. The journal publishes original clinical and experimental studies, literature reviews, clinical cases on the following topics: otorhinolaryngology, ophthalmology, plastic surgery, dentistry, neurosurgery, oncology, maxillofacial surgery, neurology, angiosurgery, anesthesiology, dermatology, endocrinology and other areas of clinical medicine. The Journal publishes the results of experimental studies.

Our aims are to (1) publish original materials that will improve clinicians' understanding of disease onset and help prevent disease in a timely manner; (2) to formulate a strategy for the prevention, diagnosis and treatment of diseases through clinical and translational research, including human genome research and new imaging techniques; (3) address issues of the relationship between experimental results and their application in clinical practice; (4) provide expert reviews of topics that keep our readers up to date on real advances; (5) to serve as a forum for general clinical and theoretical problems in the development of pathology; (6) provide helpful criticism that enables authors to improve their submissions. We believe this approach to editorial policy epitomizes the ORLHNP's commitment to providing important information that is easily interpreted by its diverse readership.

ORLHNP has been published quarterly since 2022. The journal is aimed at doctors, scientists, researchers.

Our mission. The Journal OTORHINOLARYNGOLOGY, HEAD and NECK PATHOLOGY (ORLHNP) is dedicated to the rapid publication of high-quality articles of interest to head and neck diseases specialists, whose research contributes to the development of high-quality diagnosis, treatment and prevention of head and neck diseases . The mission of the journal is using an interdisciplinary approach to integrate various studies in the field of diagnosis, treatment and rehabilitation of diseases of the head and neck organs, to contribute to the formation of new promising areas, as well as the education and development of scientists and practitioners.

Review

Photobiomodulation surgery of the soft palate

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Abstract: The purpose of the work: To familiarize specialist in the field of laser ENT surgery with the stages of the historical development of surgical care for patients with ronchopathy and obstructive sleep apnea syndrome, to evaluate the effectiveness of traditional uvulopalatoplasty metods and to justify the introduction info practice of the use of laser radiation for uvulopalatoplasty and its modifications. To increase the effectiveness of laser uvulopalatoplasty and its application in patients with ronchopathy and obstructive sleep apnea syndrome of any severity, a method of laser sculptural uvulopalatoplasty based on the use of carbon dioxide laser radiation in the "Super pulse" mode with a scanning device is proposed.

Keywords: obstructive sleep apnea syndrome, uvulopalatoplasty, CO2-laser.

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1. Introduction

It has already been 70 years since, for the first time in 1952, the "father" of the treatment of patients with snoring, the Japanese surgeon Takenosuke Ikematsu (Takenosuke Ikematsu) from the city of Noda successfully resected the hypertrophied tissues of the soft palate and his tongue to a young bride, a 23-year-old girl whose loud snoring jeopardized marriage. As a result of this surgical intervention, postoperative scars reduced the length of the soft palate, pulling it up, expanded the lumen of the upper respiratory tract at the level of the soft palate, which ultimately ensured the disappearance of snoring. This operation T. Ikematsu proposed to call uvulopalatoplasty (UPR, UPP). To date, this method has become the basis of classical traditional surgical intervention performed for the treatment of patients with ronchopathy. In 1964, T. Ikematsu surgery was recommended for all patients with uncomplicated snoring [1].

The works of Ikematsu and his followers served as the basis for a new surgical intervention. In 1981, Shiro Fujita from Henry Ford Hospital in Detroit, Michigan, modified the Ikematsu method [2]. He suggested removing not only the hypertrophied tissues of the palatine curtain, but also the palatine tonsils with their arches. He suggested calling this operation uvulopalatopharyngoplasty (UPP), which was intended for the treatment of patients with complicated ronchopathy with a clinical picture of obstructive sleep apnea syndrome (OSA) of mild and moderate severity, However, this operation was not indicated for the treatment of patients with severe OSA. To date, UPFP remains the most common method of treating patients with ronchopathy.

The effectiveness of these surgical interventions in patients with ronchopathy over the last decades of the last and the beginning of this century, according to credible foreign studies [3-10], amounted to: up to 80% in patients with ronchopathy with uncomplicated snoring, up to 50% in patients with mild OSA and less than 20% in patients with moderate OSA.

Despite the wide prevalence of these surgical interventions on the soft palate in patients with ronchopathy and OSA, they could not be considered completely satisfactory, which stimulated the continuation of the search for more effective methods of surgical treatment.

For the first time, Carenfelt C. et al. (1986) applied high-energy laser radiation in the process of performing SCP to a patient with ronchopathy [11]. The authors, dissecting the mucous membrane of the soft palate with carbon dioxide (CO2) laser radiation under local or general anesthesia, drew attention to the absence of bleeding from the wound tissues, which was represented by Carenfelt C. et al. a very attractive technology that aroused the interest of many of their colleagues.

Four years later, the French surgeon Kami N.M. (Yves Victor Kamami) [12] performed on an outpatient basis under local anesthesia for a patient with uncomplicated snoring, using CO2 laser radiation instead of a traditional surgical scalpel, i.e. for the first time he performed laser uvulopalatoplasty (DAR, LUPP). A year later, Johns M.W. (1991) reported the successful completion of the operation described by Kami Y.V. to several patients with mild to moderate OSA ronchopathy [13].

In 1993, Ellis P.D.M. proposed a more conservative, in his opinion, magnifying glass method [14], based on pulling the palatal curtain by successive scarifications. The purpose of the operation was to increase the tension of the palatine curtain by excising a narrow strip of the mucous membrane from the palatine uvula to the border with the hard palate. After laser evaporation of the tissue structures of the submucosal layer, the excised fragment of the mucous membrane was proposed by the author to be returned to its place, fixing it with separate sutures to the bottom of the wound. Similar actions were also carried out on the other side of the palatal curtain.

A year later, Farrington T. et al. [15] modified the Ellis P.D.M. operation by offering laser radiation to vaporize a narrow and long fragment of the mucous membrane with the underlying structures of the submucosal layer along the entire length of the soft palate: from the base of the palatal uvula to the border between the soft and hard palate on both its surfaces. The healing of the open wound surface occurred by secondary tension. At the same time, the scar provided tension of the palatine curtain. In the literature, the LUPP method proposed by Farrington T. with co-author, received the name "English method".

In the same 1994, Kami Y.V. published the results of the use of a magnifying glass performed on 46 patients suffering from frequent episodes of nocturnal apnea [16]. In 40 out of 46 operated patients (87%), the treatment was effective. The operation, called Krespi Y.P. [17] "the French method", was a fast, safe and very effective method of treating patients with ronchopathy and OSA.

Depending on the individual characteristics of the patient, but above all, on the severity of OSA and some other features of the disease, Kamami Y.V. used two methods proposed by him: one-stage and two-stage options.

The operation with the use of CO2 laser radiation differed favorably from traditional methods of SCP, with a very short duration, absence of blood loss and transience of inflammatory reactions of the operated tissues. At the end of all its stages, the soft palate became quite rigid, and snoring completely or almost completely stopped. Normalization of breathing during sleep and restoration of its continuity ensured full rest of the patient, which ultimately had a positive effect on his general condition, working capacity and quality of life. However, it should be noted that during the 3 weeks of the immediate postoperative period, patients complained of significant pain in the area of surgery, which was obviously due to the excessive thermal effect of laser radiation on the operated tissues.

A year later, the LOUP and its variant, the LOUP, began to be widely used by otorhinolaryngologists in many US cities. However, already in the same year, 1994, the specialists of the American Sleep Disorders Association (ASPA) proposed to limit the use of LUPP methods for the treatment of patients with ronchopathy and OSA [18].

Nevertheless, Krespi Y.P.; Lauretano A.M. et al.; Walker R.R.; Verse T. et Pirsig W.; Litter M. et al. [19-23] and some other authors, having studied the results of LUPP, came to the conclusion that it is advisable to perform this operation in patients with uncomplicated course of ronchopathy. At the same time, they strongly recommended refraining from performing magnifying glasses in patients with mild, moderate, and, especially, severe OSA.

However, by the beginning of the XXI century, a stable opinion began to be clearly formed that any surgical intervention, including laser, performed by a patient with ronchopathy with OSA, causes a deterioration in the clinical course of the syndrome, often increasing the intensity of snoring and increasing the frequency of episodes of nocturnal apnea. Many surgeons began to limit the indications for not only laser, but also traditional surgical interventions in patients with ronchopathy and OSA, and more often refuse to perform them [24-25].

The publications of Friberg D. et al had a certain influence on the formation and development of this trend. (1997, 1998) [26-27]. The results of their numerous histological studies of soft palate tissues in patients who underwent surgical, including laser, intervention for ronchopathy allowed us to assume the influence of surgical tissue trauma on the formation of disease recurrence and postoperative complications.

A little later, in 2010, the American Academy of Sleep Medicine (AASM) proposed a resolution on the need to develop standards for evaluating the effectiveness of treatment methods for patients with ronchopathy and OSA. They were recommended to conduct a sociological study without fail, at least twice. The first was intended for the primary diagnosis of OSA and clarification of its severity, and the second – for an objective assessment of the effectiveness of the treatment method.

Despite the restrictive recommendations, an active search for new, other effective methods of treating patients with ronchopathy was actively continued. The development and popularization of laser technology, the emergence of new laser radiation generators, the discovery of the effects of the influence of specific characteristics of laser radiation on various tissues and environments of a living organism have certainly stimulated the development of laser surgery, including the development of new laser operations on upper respiratory tract tissues.

Finkelstein Y. et al. (1997) [28] compared the results of the use of UPP and UPP performed in 174 patients with severe OSA with ronchopathy. At the same time, 100 patients underwent surgery

using the traditional method, and 74 – using a CO2 laser. It was found that in patients who underwent a magnifying glass, in the postoperative period, the pain syndrome was more pronounced and bothered significantly longer than in patients who underwent traditional SCP. After LUPP, the authors noted the effect of "circular" scarring of soft palate tissues in patients, which led to a decrease in the airway lumen at the level of the palatine curtain. In their opinion, the appearance of scar tissue is due to the effect of excessive laser radiation, which caused excessive local thermal damage to the operated tissues.

Remacl M. et al. (1999) [29] used a "Sharplan" CO2 laser model capable of generating radiation with a power of up to 15 watts in the SuperPuls (SP) mode: that is, the generation of ultrahigh-frequency radiation pulses that can be used both in constant and any of the modulation modes. This technical capability made it possible to minimize the thermal load on the tissues surrounding the evaporated fragment, and, consequently, to significantly reduce pain in the patient during the operation and in the postoperative period, to shorten the healing time of the laser wound, ensuring its healing by restitution, and reducing the possibility of scar tissue development in the wound. At the same time, dissection and evaporation of tissues by carbon dioxide radiation in the SP mode completely preserves the hemostatic effect, making the operation as bloodless as when using the usual radiation mode.

Performing layer-by-layer ablation (evaporation) of a rectangular or rounded portion of the mucous membrane and structures of the submucosal layer from the base of the uvula to the palatine fossa of the anterior (oral) surface of the soft palate, Remacl M. et al. the surface of the soft palate muscle was left intact. Then they coagulated and vaporized the tissues of the distal third of the tongue and vaporized the velar arches. The coagulation of tissues was carried out with a defocused beam, and their vaporization (evaporation) was carried out with maximally focused radiation generated on the surface in the SP mode.

The magnifying glass method proposed by Remacle M. et al. and combining the advantages of English and French methods, but avoiding their potential drawbacks, was designed to carry out laser correction of palatal curtain tissues. Therefore, like previous researchers, the authors recommended using it to treat patients with uncomplicated snoring.

Nevertheless, based on the research results of Finkelstein Y. et al. [28]; Lauretano A.M. et al. [20]; Verse T. et Pirsig W. [22]; Email M. et al. [29]; Littner M. et al. [23]; and a number of other publications devoted to the analysis of the results of traditional and laser surgical interventions performed to relieve patients from night snoring, AASM came to the conclusion about the equivalent effectiveness of traditional surgery and LUPP in patients with uncomplicated snoring. It was also pointed out that the presence of even a mild degree of OSA should be considered as a contraindication to performing both traditional and laser surgery.

It cannot be excluded that this recommendation was partly due to the lobbying of manufacturers of devices designed and intended for the treatment of patients with ronchopathy and OSA by creating an increased pressure of the air flow passing through the upper respiratory tract of a sleeping person, i.e. for the implementation of so-called CPAP therapy and some other devices to combat snoring by non-surgical methods. Unfortunately, this trend continues to be observed to this day.

However, the already accumulated experience of using LUPP in patients with ronchopathy and, even, OSA, demonstrates the absence of blood loss and the short duration of laser surgery, the transience of postoperative inflammatory processes that occur during surgical trauma of the mucous membrane and underlying tissues, the safety of surrounding tissues, gradually, as clinical observations accumulate, which contributes to an increase in the number of supporters, convinced of the expediency and effectiveness of the use of laser radiation as the main surgical instrument when performing SCP and UPFP in patients with mild and moderate OSA, and in some cases, severe [30-37].

In order to prevent the effects of excessive power of carbon dioxide laser radiation, attempts were made to use the radiation of solid-state, semiconductor and other lasers, a wide variety of which by this time had already found application in other areas of surgical practice. The search for optimal laser radiation in all respects and the devices that generate it continues to the present time.

In 2002, Blotsky A.A. and Pluzhnikov M.S. [38] proposed to use Nd:YAG laser radiation, the active substance of which was an artificially grown garnet crystal with alumoittrium and neodymium additives. Radiation from the generator to the surface of the operated tissue is transmitted via a quartz polymer fiber. The authors have provided three options for their proposed method of operation. The choice of each of them depends on the characteristics of the pathological processes occurring in the tissues of the soft palate, and the individual characteristics of the patient.

In order to minimize surgical damage to the soft palate tissues and at the same time enhance its rigidity, V.F. Melnik (2003) [39] proposed not to dissect, but to coagulate the tissues of the back and front surfaces of the soft palate by pinpoint exposure to somewhat defocused Nd:YAG laser radiation. The depth of tissue coagulation did not exceed 4-5 mm. The parameters of laser radiation and the time of its exposure at each specific point were determined by the operating

surgeon depending on the nature and severity of pathological processes occurring in the tissues. According to the author, an adequate choice of laser radiation energy for point photocoagulation not only minimizes tissue injury, but also determines the optimal characteristics of the forming scars, which further ensure the sufficiency and uniformity of the compaction and tension of the palatine curtain.

For the treatment of patients with ronchopathy and OSA Karpishchenko S.A. et al. (2014) [40] carried out LUPP using radiation with a wavelength of 0.8-1.06 microns generated by models of LED lasers. The operation, the course of the postoperative period and the evaluation of the effectiveness of treatment in patients with ronchopathy and OSA in general were similar to the technique of performing surgery with Nd:YAG laser radiation.

Fotona company proposed to use radiation with a wavelength of 2940 nm generated by an Er:YAG laser for the treatment of patients with ronchopathy and OSA and patented a method for the treatment of patients with ronchopathy "NightLase" (2011) [41]. To achieve the effect of point coagulation, 7 to 15 thousand radiation pulses per session were applied to the tissue surface. To achieve a stable therapeutic effect of point laser coagulation by pulsed radiation of the Er:YAG laser, it is necessary to repeatedly, at intervals of 2 to 6 weeks, expose the tissues of the soft palate, anterior and posterior palatine arches, palatine tonsils and lateral surfaces of the tongue. The undoubted advantage of this method was the absence of the need to perform preliminary anesthesia of the tissues to which the laser effect will be applied and the easy tolerability of this surgical laser intervention by patients. The disadvantages of the method include the duration of treatment, due to the need for at least three sessions of laser exposure with intervals between them from 15 to 45 days.

At the same time, the radiation of erbium, both neodymium and semiconductor lasers from the source to the surface to be affected is transported through a fiberglass fiber. At the same time, a loss of radiation power naturally occurs. At the exit from the light guide, the radiation becomes defocused, which significantly reduces the density of the energy absorbed by the tissues and requires an increase in the exposure time to achieve coagulation of each specific tissue site. This significantly complicates the rational choice of the parameters of the laser radiation used, which ultimately determine the final result of this surgical intervention.

Simultaneously with the search for new LOUP methods based on the use of laser radiation generated by solid-state and semiconductor laser installations, the search for improvement of LOUP methods using carbon dioxide laser radiation continued.

In 2019, Camacho M. et al. proposed their own version of the LUPP [42]. Using CO2 laser radiation, the authors removed a small fragment of the mucous membrane of the lower edge of the soft palate, while retaining the tongue, which was fixed to the remaining part of the palate, after which a bilateral tonsillectomy was performed, stitching the anterior and posterior palatine arches (palatine and palatopharyngeal muscles). After surgery, the rigidity of the palatine curtain significantly increased in patients, which contributed to a decrease in the intensity of snoring until its complete cessation.

In 2021, V.B. Knyazkov et al. [43] proposed a new original method of laser sculptural uvulopalatoplasty (uvulopalatopharyngoplasty) (LSUPP, LSUPFP) using carbon dioxide laser radiation (RF Patent for invention No. 2760295 of 12.04.2021). A preliminary study of the results of its clinical application showed the safety of the proposed method of surgical intervention on the soft palate and its sufficiently high effectiveness in patients with ronchopathy, even with severe OSA.

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Article

Comprehensive rehabilitation of patients after septoplasty

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Abstract: The aim of the work was to evaluate the effectiveness of the use of photobiomodulation therapy (PBMT) in combination with Respiro Mirtol forte in order to improve the rehabilitation period of patients after septoplasty. 92 patients underwent septoplasty under general anesthesia (55 men and 37 women, age ranged from 18 to 46 years), followed by tamponade of the nasal cavity. Patients of the 1st group did not undergo PBMT; in patients of the 2nd group, PBMT was performed 3 hours, 6 hours and 24 hours after septoplasty (infrared pulsed laser radiation, λ = 0.890 μm, P = 10 W, 2 minutes in the projection of the wings of the nose); Patients of the 3rd group were given PBMT in the indicated regimen and Rispiro Mirtol forte 5 days before and within 10 days after septoplasty. In 48 hours, after removing the tampons, in patients of the 2nd and 3rd groups, intranasal PBMT was used with a nozzle in the red range, with λ = 0.63 μm, P = mW, for 2 minutes. Heart rate variability (HRV) was assessed: ultra-low frequencies (ULF), high frequencies (HF), low frequencies (LF) and total power of heart rate variability (HRV), pain syndrome. ULF, LF, HF, total HRV power were significantly lower in group 2, compared with group 1, but higher than in group 3. In the period from 6 to 24 hours after septoplasty, the patients of the 1st group experienced a pain syndrome of greater intensity than the patients of the 2nd and 3rd groups ($p < 0.001$). The patients of the 3rd group had minimal pain values compared to the 2nd group. Thus, the use of PBMT in combination with Respiro Myrtol forte in the postoperative period after septoplasty against the background of nasal tamponade helps to minimize pain, reduce inflammation in the area of surgical damage, and, consequently, less pronounced changes in the autonomic nervous system in response to surgical stress.

Keywords: septoplasty, pain, photobiomodulation, heart rate variability, Respiro Mirtol forte.

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1. Introduction

Surgical correction of the curved nasal septum (IPN) – septoplasty – is one of the most common operations in rhinosurgery. Frequent complications after septoplasty are nosebleeds, nasal septum hematoma, acute rhinosinusitis and pain syndrome [1, 2]. After septoplasty, hemorrhagic and purulent-mucous crusts may form, under which the secret of the mucous glands may accumulate, which aggravates the rehabilitation period after septoplasty [3]. Septoplasty consists in the separation of the muco-suprachrachial and /or muco-periosteal leaves and the removal of curved areas of the cartilaginous and / or bony parts of the nasal septum. As a rule, smooth sections of the extracted cartilaginous part of the nasal septum are placed back between two leaves of the suprachristle. At the same time, the nasal cavity is tamponed after surgery to avoid complications [4].

A special position is occupied by the issue of rehabilitation of patients after septoplasty, which includes high-quality anesthesia, analgesic therapy, the use of local medicines. For example, we have previously demonstrated that septoplasty by itself [5], as well as with poor–quality anesthetic aid, provokes the development of a distress syndrome - an imbalance of the autonomic nervous system, severe pain syndrome and a violation of the quality of life in the early postoperative period, which is confirmed by changes in the balance of the autonomic nervous system (ANS) and changes in heart rate variability (HRV) [6].

To reduce the manifestation of side effects after septoplasty (pain, swelling of tissues, inflammation, ecchymosis, etc.), photobiostimulation has been increasingly used recently [67], which improves and accelerates tissue repair, and consequently, the healing of surgical wounds. These photobiostimulation effects are based on improving intracellular calcium metabolism and accelerating the synthesis of adenosine triphosphate in mitochondria [8, 9]. Photobiomodulation therapy (FBMT) is a form of light therapy. PBMT uses non–ionizing light sources, such as lasers or light-emitting diodes (LEDs) with a wavelength of 0.6-1 microns and a power of less than 500 MW per diode [10], to cause a photochemical reaction that leads to an increase in ATP synthesis in mitochondria, signal transmission in biological membranes and cells, DNA synthesis, proliferation cells, differentiation and modulation of pro- and anti-inflammatory mediators, leading to a decrease in pain and inflammation [11-13]. PBMT is widely used for the treatment of various diseases – diabetic ulcers, blood diseases, musculoskeletal complications, coronary heart disease, as well as for wound healing, pain and inflammation reduction, tissue repair and regeneration [14, 15].

A review of the literature shows that after septoplasty, FBMT is applied intranasally after the removal of tampons, or immediately in the case of splints [16]. At the same time, there is practically no data where the effectiveness of PBMT was evaluated when exposed during tamponade in the first two days after septoplasty.

Considering the above data, this study was conducted to evaluate the effectiveness of photobiomodulation therapy in combination with the use of Respiro Myrtol forte in order to improve the rehabilitation period of patients after septoplasty.

2. Patients and Methods

2.1. Rhinosurgery.

92 patients underwent septoplasty under general anesthesia. Among them there were 55 men and 37 women aged 18 to 46 years. The patients were randomly divided into 3 groups. The first group included 30 patients who did not use FBMT and did not use Respiro Myrtol forte 5 days before and 10 days after septoplasty, 1 capsule 3 times a day. There were 31 patients in the 2nd (group with PBMT) and 3rd groups (group with a combination of FBMT and Respiro Myrtol forte). Women underwent septoplasty during the periovulatory period, as it is known that it is during this phase of the ovarian-menstrual cycle that the risk of nosebleeds after rhinosurgery is minimal [17]. Immediately after the operation, all patients had an anterior nasal tamponade with gauze swabs in glove rubber for 1-2 days. All patients underwent septoplasty using local infiltration anesthesia with 1% procaine solution (250 mg) together with 0.1% epinephrine solution (10 mg) and general anesthesia, for which fentanyl (30 mcg/ml), propofol (150 mg), cisatracuria bezilate (nimbex) (6 mg), tranexamic acid was used (tranexam) (1000 mg), atropine (0.5 mg) and metoclopramide (cerucal) (10 mg). In order to prevent the development of acute bacterial inflammation of the paranasal sinuses, oral antibacterial therapy of azithromycin 500 mg once in the morning for three days with the first intake in the morning on the day of surgery was prescribed.

2.2. PBM therapy.

After 3 hours, 6 hours and 24 hours after septoplasty, patients of the 2nd and 3rd groups underwent laser therapy. The emitter heads generated infrared pulsed laser radiation with a wavelength of 0.890 microns and an installed power of 10 watts (LASMIC-01 apparatus, Russia). The emitter heads were installed in the projection of the lateral cartilage and the large cartilage of the nose wing on both sides for 2 minutes.

24-48 hours after surgery, nasal tampons were removed in patients of both groups and in groups 2 and 3, intranasal PBMT with a nozzle was performed in a continuous, modulated mode of operation in the red optical range, with a wavelength of 0.63 microns and with a radiation power of 8 MW. The heads were installed in both halves of the nose for 2 minutes (the device "LAZMIK-01", Russia).

2.3. HRV and pain syndrome analysis.

To assess heart rate variability (HRV), a daily Holter electrocardiogram (ECG) was recorded using MT-200 devices (Schiller, Swiss). The ECG recording system was installed in patients 30 minutes before septoplasty and removed 24 hours after it. The parameters of HRV in the frequency range were studied – low frequencies (LF, ms2), ultra-low frequencies (ULF, ms2), high frequencies (HF, ms2) and total power (Total power, ms2).

Pain syndrome was assessed using a visual analog scale [5] (Fig.1) 1, 3, 6, 12, 24 and 48 hours after septoplasty, and in group 2 immediately after laser therapy sessions. Patients were asked to place a vertical line or dot at the point on the scale that they thought corresponded to the pain they were experiencing. The scale length was 100 mm. The intensity of pain was measured in mm.

Figure 1. Visual-analogue scale for assessing the intensity of acute pain syndrome.

2.4. Statistical analysis.

All statistical data processing was performed using the HASP software package, version 0.14.0 (University of Amsterdam, The Netherlands) for Windows®. Continuous variables (pain magnitude, LF, ULF, HF, Total power) were presented as the mean±error of the mean (M±SE) and analyzed using the t-test of independent samples after checking normality using the Shapiro-Wilk test. Normally distributed data were evaluated using the Student's t-test of independent samples, and abnormally distributed data were evaluated using the Mann-Whitney U-test. The values of $p<0.05$ were considered statistically significant.

3. Results

3.1. Heart rate variability.

After the PBMT sessions, the ultra-low frequency component of HRV spectral analysis was significantly lower in the 2nd group (8086±3003 ms2), compared with the first (18580±2067 ms2) ($p<0.001$) (Fig. 2a). The low-frequency component of HRV was significantly higher in the 1st group (1871±405 ms2), compared with the 2nd (1095±190 ms2) ($p<0.005$), which indicates an increase in the tension of the sympathetic part of the ANS in the group without the use of PBMT (Fig. 2b). Based on the analysis of the high-frequency component of HRV, a decrease in the activity of the parasympathetic nervous system during the perioperative day was also recorded in the 2nd group as a whole – 1157±220 ms2 versus 1630±263 ms2 in the 1st group ($p<0.01$) (Fig. 2b). In group 2, the total HRV power was significantly lower (13498±3226 ms2) than in group 1 (26808±2371 ms2) ($p<0.001$) (Fig. 2g). In the third group, the total power (9502±2508 ms2), the ultra-low-frequency component (4722±1595 ms2), the low-frequency component (664.57±156.61 ms2) and the high-frequency component (899±135 ms2) were significantly lower than in the second group ($p<0.01$).

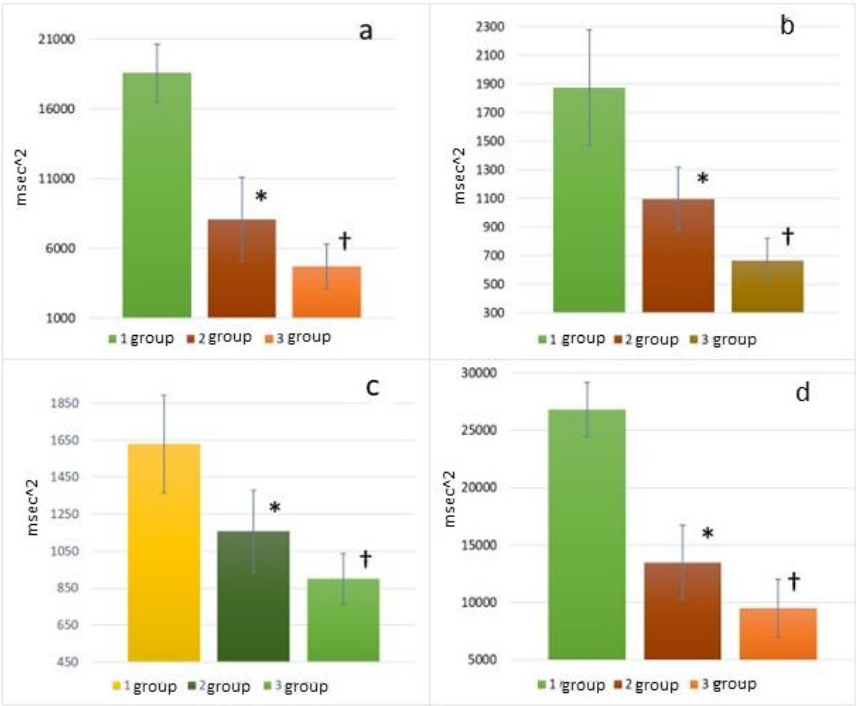

Figure 2. Changes in the frequency of heart rate variability with the use of PBMT after septoplasty and without it: a-ULF, b-LF, c-HF, d-Total power. The error bars indicates standard error.

3.2. Pain syndrome.

In the first 3 hours after surgery, the intensity of pain severity did not differ between the groups ($p=0.07$). In group 1, the intensity of pain increased after 6 hours compared to 3 hours after

surgery, but no significant difference was recorded (p=0.01). After 6 hours in group 2, the intensity of the pain syndrome began to decrease compared to the previous period (p<0.05) (Fig. 3). Patients of group 3 experienced pain significantly lower than patients of group 2 from the 3rd hour after surgery (Fig. 3, Table. 1). Further, the pain syndrome continued to decrease in all groups and 48 hours after septoplasty, patients did not feel pain. At the same time, in the period from 6 to 24 hours after surgery, group 1 patients experienced pain significantly higher than patients with PBMT and a combination of PTMT and Respiro Myrtol forte (p<0.001) (Fig. 3, Table 1).

Table 1. Intensity of acute pain syndrome after septoplasty.

Time after surgery	1 hour, mm	3 hours, mm	6 hours, mm	12 hours, mm	1st day, mm	2nd day, mm
1 group	17,15±2,46	21,82±2,83	25±2,02	21,64±2,36	16,68±1,01	3,68±1,01
2 group	14,16±2,31	18,88±2,45	16,43±2,08	12,83±2,38	10,84±1,15	3,84±1,15
3 group	10,33±1,99	15,31±2,43	11,75±2,14	10,012,06±	3,44±0,98	2,55±1,96

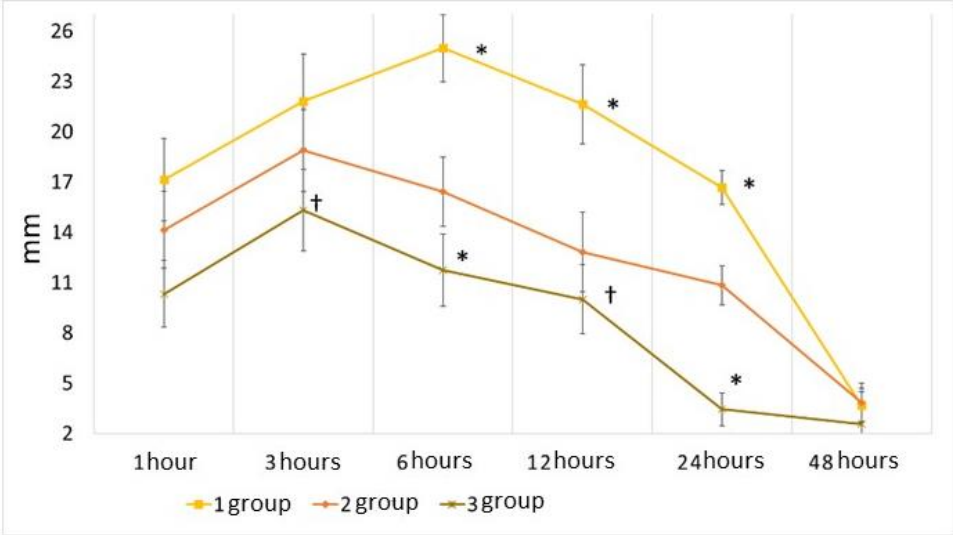

Figure 3. Intensity of pain syndrome after septoplasty. * – significant differences between groups at p<0.001, † – significant differences between groups at p<0.01.

4. Discussion

It is known that removal of tampons is advisable no later than 2 days after surgery, when the inflammatory processes decrease and at the same time the restoration of the mucous membrane begins, normalization of blood supply to cartilage and bone tissues [1, 2], therefore, we considered it important to use PBMT during the first 2 days. In the available literature, we have not found any works where PBT would be performed in patients after septoplasty with intra-nasal tampons and with a high frequency of therapy sessions on the first day after rhinosurgical interventions.

The generally accepted theory of the mechanism of biological effects of PBM is the absorption of light by chromophores [18]. PBMT leads to the following effects: reduction of edema and inflammation, reduction of pain, collagen synthesis, increased elasticity, increased tissue perfusion and increased tissue vascularization, increased cell proliferation, especially fibroblasts, which generally leads to the restoration of damaged tissues [7]. Recent studies have shown that PBMT is effective in various conditions from diabetic foot to androgenic alopecia and mucositis after chemotherapy, as well as in wound healing and inflammation [8, 9, 18-20]. PBMT can play a role in reducing the number of new hemorrhages after surgical interventions in the maxillofacial region. At the same time, PBMT is positioned as a new alternative to other interventions since it is an easy-to-use and minimally invasive method [7].

Hersant et al. the effect of a low-intensity laser on the results of flap survival in facial plastic surgery was evaluated. The authors have shown that PBMT promotes higher survival of the flap, accelerates wound healing [20]. Enwemeka et al. It was found that PBMT with high efficiency promotes the restoration of damaged tissues during all three phases and reduces pain syndrome [22].

The effects of PBMT described above, especially the restoration of damaged tissue and neovascularization, provide a reduction in edema and inflammatory reactions, a decrease in the likelihood of hemorrhage [7] and, consequently, pain in the tissue after septoplasty. With the intranasal application of laser therapy, systemic effects are also achieved through cells and blood components [23], which can probably contribute to a positive neurotherapeutic effect [24]. The tissues around the nasal cavity have an abundant blood supply with relatively slow blood flow. It has been shown that PBMT improves blood rheology [25], reduces blood viscosity [25] and improves blood clotting status [27] in various pathological conditions. In group 2 patients, a significantly lower intensity of pain syndrome, a decrease in power compared to group 1 patients, indicates relatively low inflammatory reactions from the blood system in the damaged area after the use of PBMT [28].

In patients with the use of PBMT, HRV indicators had significantly lower overall power compared to patients without laser therapy. Thus, an ultra-low frequency component, which is often associated with circadian rhythms [29]. An increase in ULF power indicates a failure of circulatory rhythms because of surgical traumatization against the background of inflammatory phenomena in the group without the use of PBMT. The high-frequency component (HF) component of HRV shows the tone of the parasympathetic nervous system, while LF, according to a number of authors, can reflect both sympathetic (mainly) and parasympathetic tone [30]. The decrease in LF and HF after septoplasty with the use of PBMT reflects a decrease in sympathetic and parasympathetic tone after correction of IPN. The shift in the balance of the ANS towards its sympathetic component is physiologically justified and corresponds to the degree of severity of stress factors. However, an increase in the tone of the parasympathetic nervous system under stress may indicate an inadequate response of the body and correspond to [31], which may reflect the degree of surgical damage in the maxillofacial region [32]. Thus, it has been shown that after LF septoplasty, HRV can decrease sharply [30]. In our study, in a group of patients with the classic variant of postoperative rehabilitation, the activity of both the sympathetic and parasympathetic parts of the ANS was increased. Studies have shown a relationship between blood rheology, cognitive functions [28] and mood improvement [33]. It has been suggested that the systemic effects of PBMT after blood irradiation may also ultimately have a neuroprotective effect [24, 34, 35]. It is also known that intranasal blood irradiation has the same neurological consequences as intravenous or intravascular PBMT [36]. These facts may also give an understanding of a lower pain syndrome, smaller changes in the balance of the ANS in response to surgical damage after septoplasty in patients with the use of PBM in the early postoperative period.

Surgical traumatization of the nasal septum inevitably leads to secondary infection of the nasal cavity [37]. In addition to bacteria, fungal invasion can also occur [38, 39]. The European Society of Rhinologists recommends the use of phytopreparations in the complex treatment of acute bacterial and viral infections in the nasal cavity and paranasal sinuses [40]. The components of Respiro Myrtol forte have both antibacterial and antimycotic effects, improve the activity of the cilia of the pseudomonas epithelium lining the nasal cavity [41]. In a study in which patients were given standardized ivy leaf extract syrup along with nasal flushing, a statistically significant smaller number of nasal secretions was reported compared to those who were only flushed with saline solution. In addition, an endoscopic examination of the nasal cavity on the sixth day after removal of the nasal tamponade showed a statistically significant lower number of nasal secretions in patients who were injected with standardized ivy leaf extract syrup along with nasal rinsing. A statistically positive correlation was found between the subjective assessment of nasal secretion by the patients themselves and the results of nasal endoscopy. In the group that underwent only nasal lavage, five patients required antibacterial therapy on the sixth day after the removal of tampons. In the group receiving standardized dry ivy leaf extract, antibacterial therapy was not required. This difference was statistically significant [41]. The guideline for the introduction of antibacterial therapy was the appearance of a purulent secretion in the nasal cavity along with an increased body temperature (more than 38 °C) and a feeling of pain or pressure in the face area, more often on one side [42]. P. Federspil et al. using the example of treatment of acute non-purulent rhinosinusitis with secretolytic myrtol and vasoconstrictor xylometazoline for 6 days, it was shown that there was a significant decrease in mucus secretion, compared with the group that received placebo together with a vasoconstrictor [43]. In the myrtol group, 7.3% of patients needed antibiotic therapy, while in the placebo group, antibiotics therapy was required in 12.6% of patients. Tarantino et al . the advantages of secretolytic administration compared to placebo in eliminating nasal secretion in patients with rhinosinusitis have been reported, while Z. Szmeja et al. it was confirmed that secretolytic administration together with standard therapy shortens the duration of

recovery in patients with rhinosinusitis [44, 45]. P. Federpil et al. [46] studied the efficacy of myrtol, an herbal extract from essential oils, as a therapeutic alternative for acute rhinosinusitis (n = 331), compared with placebo and other essential oils. The results showed a statistically significant improvement and decrease in the total number of rhinosinusitis symptoms in the standardized myrtol group and the group of other essential oils, compared with placebo, after 14 days (10.5 vs. 9.2 points) with no difference between myrtol and other essential oils. The decrease in the intensity of the pain syndrome, the low power of HRV indicators in patients of group 3, compared with group 1, confirm the effectiveness of the strategy of comprehensive rehabilitation of patients in the postoperative period who underwent septoplasty.

5. Conclusions

Accordingly, the use of FBMT in combination with Respiro Myrtol forte in the postoperative period after septoplasty against the background of nasal tamponade helps to minimize pain syndrome, reduce inflammatory processes in surgical damage, and, consequently, less pronounced changes in the autonomic nervous system in response to surgical stress.

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Article

The role of autonomic nervous system imbalance in the pathogenesis of hyperplastic laryngitis

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Abstract: A decrease in the mediator activity of nerve structures in organ tissues leads to the development of neurodystrophic changes and an increase in their sensitivity to certain influences. In these planets, it is important to assess the morphological characteristics of target structures, taking into account the neurodystrophic component of the disease. The aim of the study was to determine the activity of the peripheral adrenergic link of the trophic reflex and assessing the morphological features of the mucous membrane of the vocal folds in chronic hypertrophic laryngitis in patients with neurovegetative disorders. Materials and methods: the study involved 45 patients (37 men and 8 women) aged 23 to 72 years with a diagnosis of chronic hypertrophic laryngitis. An objective study of the upper respiratory tract, a cytological study of reprinted smears from the affected areas of the larynx, a study of the functional state of the ANS, as well as a histological and histochemical study of the removed tissue were carried out. Results. The examined patients were found to have dysfunction of the ANS in the form of insufficient or excessive autonomic support of activity. Morphological signs of keratinization of the epithelium of the mucous membrane of the vocal folds and its active proliferation, as well as dystrophic and atypical changes in cellular elements revealed as a sign of insufficient, tact and a sign of excessive vegetative support of activity. It was found that with insufficient vegetative support of activity, the proliferative activity of epithelial cells is more pronounced than that of a chemer with excess. The same applies to keratosis with atypia and dystrophic changes in the epithelium. Conclusions. The activity of the interstitial adrenergic nerve structures of the mucous membrane of the vocal folds correlates with the characteristics of autonomic activity. The weakening of the processes of synthesis, accumulation and excretion of neurotransmitter is associated with insufficient vegetative support of activity, and their strengthening is associated with excessive. The amount of neurotransmitter in peripheral nerve fibers and endings depends on the nature and intensity of manifestations of neurogenic dystrophies developing in executive tissues – targets of adrenergic innervation.

Keywords: hypertrophic laryngitis, vegetative disorders, adrenergic nerve fibers, neurogenic dystrophy.

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1. Introduction

Ideas about the neurodystrophic component of the pathogenesis of various diseases, regardless of their causal origin, appeared as a result of the creation of the doctrine of nervous trophism and nervous dystrophy [1]. They are based on convincing evidence of the role of neural mechanisms in ensuring morphofunctional transformations in the body [1-3].

It has been established that under the action of any pathogenic factor in the body, the trophic function of the autonomic nervous system (ANS) is activated, the state of which determines the course and outcome of a specific pathological process associated with the degree of damage to adaptive, compensatory-adaptive and protective mechanisms [4-6]. The nervous system exercises control over reproduction, growth, development, differentiation of the cell of the organism, the

formation of their communities, the timing of their life and ghibellines [3, 5]. At the same time, the influence of the nervous system on metabolic processes in tissues that are targets of efferent innervation is understood as a trophic function. The weakening of trophic function causes not only dystrophic changes in target structures, spout and cell dedifferentiation in different tissues [2, 3, 7].

To date, it is known that trophic regulation is carried out by reflex [1] and autonomic nerve fibers perform their trophic function with the help of neurotransmitters of the autonomic nervous system (VNS). Such neurotransmitters include catecholic amines: norepinephrine (NA), adrenaline (A), dopamine (DA), indole amine serotonin (CT), acetylcholine (AH), histamine (G), gamma aminobutyric acid (GABA) and others. Among them, the most studied are the neurotransmitters of the sympathetic and parasympathetic divisions of the ANS - NA and AH. A decrease in the mediator activity of nerve structures in the tissues of one or another organ, as well as partial libor complete denervation, lead to an increase in its sensitivity to certain influences [3, 8-10]. This phenomenon is called denervative hypersensitivity [4, 11] and requires its study in the further development of an algorithm for the most effective therapeutic measures. In this plan of materiality, it is also important to identify the morphological features of the target structures, taking into account the neurodystrophic component of a particular disease.

The purpose of this study was to determine the activity of the peripheral adrenergic link of trophic reflexion and to identify morphological features of the mucous membrane of the vocal folds in patients with chronic hyperplastic laryngitis in patients with neurovegetative disorders.

2. Patients and Methods

During the examination of patients who applied to the phoniatric department of the St. Petersburg Research Institute of bump, throat, nose and recited about violations of voice function, in 45 cases (37 men and 8 women aged 23 to 72 years), a clinical diagnosis was made: "chronic hyperplastic laryngitis" In all patients of the former, informed consent was obtained over the expansion of the volume diagnostic measures in comparison with established standards. During the examination, an anamnesis of the disease was collected, a video stroboscopy of the larynx was performed, a cytological examination of smear prints [12] from the mucous membrane of the affected areas of the vocal folds was performed, the functional state of the ANS was assessed using the ANS–spectrum device, whose work is based on the analysis of heart rate variability. Studies of the activity of the ANS were carried out in conditions of complete comfort and determined vegetative tone (VT), vegetative reactivity (VR) and vegetative maintenance of activity (VOD). The results of a similar study on the same device of vegetative parameters in 20 healthy volunteers (15 men and 5 women) were used as benchmarks. Numerical indicators of CIG and hemodynamics obtained in healthy people were taken as control and their changes in the examined patients were taken into account. At the same time, VT was considered normal (eitonia), reduced or increased (hypo – and hypertonus), BP – normal, or increased (hyperreactivity), or reduced (hyporeactivity) and VOD – adequate, excessive or insufficient. These signs are the criteria on the basis of which the functional activity of the ANS is assessed at the system level.

In some patients, hypertrophied areas of the vocal folds had the appearance of tumor-like formations. To correct the voice, these areas were strangled under the control of a video stroboscope, under local anesthesia (10% lidocaine solution), with preliminary premedication with atropine 0.1% and promedol 2%. At the same time, one part of the surgical material was treated according to the traditional histological technique and stained with preparation hematoxylin and eosin in order to make a morphological diagnosis. Another part of the material was used to stage a histochemical reaction. Adrenergic nerve structural was detected by incubating frozen sections in a 2% dissolution of glyoxylic acid (C2H2O3*H2O – glioxylic acid monohydrate 98%, manufactured by the company Fluca A.G., Switzerland), which forms intensity luminescent compounds with biogenic amines in tissues. After setting up the histochemical reaction, the preparation was studied in a luminescent microscope LUMAM-P8 (using a light filter with a free length of 480 nm) and using a photometric nozzle FMEL-1A, the intensity of luminescence (IL) of adrenergic nerve structures was measured, which reflects the degree of their activity.

Cytological preparations were stained according to the hematological method: Maya–Grunwald dye-fixative nao 3 minha was applied to glasses with smears - prints, then it was washed with running water from the back of the glass and the smears were painted according to the Romanovsky method for 10 – 15 min.

Statistical processing of the research results was carried out using Windows 7 software using Microsoft Excel 2010 programs. The Spearman correlation coefficient was calculated, which makes it possible to determine the closeness (strength) and direction of the correlation link between two signs or two profiles (hierarchies) of signs.

3. Results

When collecting the medical history, it was found out that 27% of patients with "chronic laryngitis" had concomitant diseases: bronchial asthma, chronic rhinitis, osteochondrosis, hypertension. Most of the patients had a bad habit of smoking tobacco. All patients complained of persistent hoarseness, some of burning sensation, dryness in the throat. The duration of the disease was: from 2 months to 10 years.

During clinical examination, it was found that the mucous membrane of the vocal folds in patients looked thickened, had a rod bloom, sometimes with a pronounced vascular pattern. Areas of hypertrophy were more often located in the anterior and middle third of one or two vocal folds, had a diffuse or limited appearance. There were signs of keratinization of the mucous membrane (Fig. 1).

During videostroboscopy, all patients had a decrease in the amplitude of vibrations of the vocal folds. The mucous bagpipe was often absent on the side with hypertrophic changes. Non-vibrating areas and areas with signs of leukoplakia were determined.

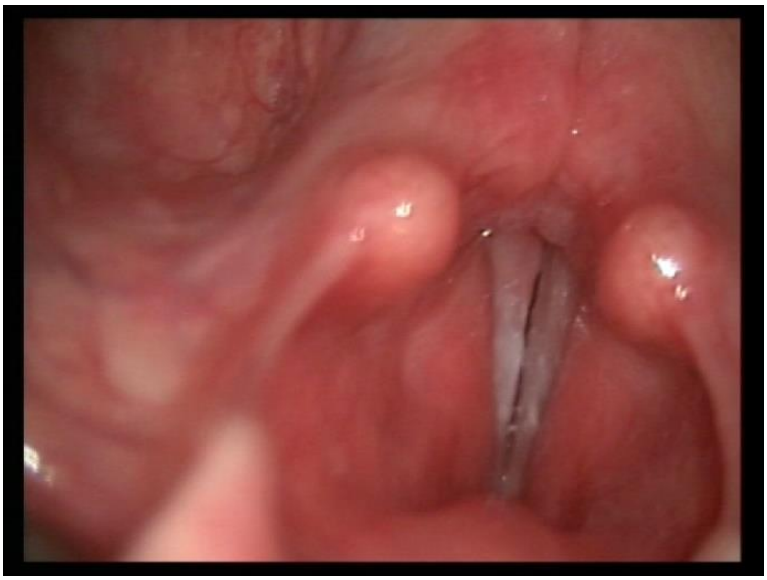

Figure 1. Videoendoscopic picture of the larynx of a patient with chronic hyperplastic laryngitis

In the study of the functional state of the ANS, dysfunction of the autonomic nervous system in the video of insufficient VOD was found in 35 (77.8%) patients, and excessive - in 4 (8.9%). In 6 (13.3%) cases, adequate VOD supply was provided by increased VT in combination with reduced vegetative reactivity (vegetative dystonia), or increased BP (vegetative hyperreactivity) and vegetative hypotension.

The activity of peripheral adrenergic nerve fibers localized in the mucous membrane of the vocal folds was evaluated using histochemical examination of the surgical material. It showed that in its own plate of the mucous membrane there are adrenergic nerve fibers that are located singly or form fine-grained terminal plexuses with weak luminescence. The luminescence intensity (IL) reflecting the neurotransmitter content inside the adrenergic nerve fiber was 19.6±0.02 rel. units. in varicose veins and 6.6 ± 0.03 rel. units in the intervaricose joints. Such a distribution of IL along the course of the studied fibers indicates their low functional activity and, consequently, a deficit of neurogenic support for the activity of executive tissues at the local level [1]. In excess VOD, a dense network of nerve plexuses of adrenergic nerve fibers with a more pronounced specific luminescence was found (Fig. 2), their IL was 38.35 ± 0.005 relative to food. in varicose veins and 12.7 ± 0.01 rel. units in the intervaricose joints. These signs reflect the activation of the adrenergic link of trophic reflexion and indicate an increased content of neurotransmitter in peripheral nerve fibers.

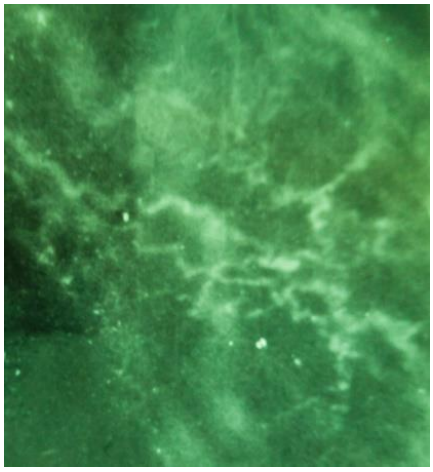

Figure 2. Luminescent adrenergic nerve fibers in the mucous membrane of the vocal folds in chronic hyperplastic laryngitis. The method with glyoxylic acid, (x200)

The close relationship of the functional state of the ANS with the luminescence intensity of peripheral adrenergic nerve fibers was revealed using the Spearman correlation coefficient (p), which was equal to 0.85 at $p<0.05$, to reflect the statistically significant dependence of the IL of adrenergic nerve fibers on the state of the ANS.

With a standard histological examination of the surgical material in all cases, the diagnosis was "chronic laryngitis with focal hyperplasia of the multilayer plateau of the epithelium". The mucous membrane of the vocal folds is a multi-layered carnal non-corneating epithelium that lies above its own plate, consisting of connective tissue. In addition to nerve fibers, it contains numerous elastic connective tissue fibers and blood capillaries. In histological preparations, areas of epithelial proliferation, its excessive keratinization with the focal location of the horny masses on the surface of the epithelial cover and thickening of the epithelial layer due to epithelial hyperplasia were detected. In some cases, flattened cells of the surface layer with basophilic cytoplasm and a large, centrally located nucleus showed signs of metaplasia. Enlarged full-blooded capillaries drew attention to themselves (Fig.3), extensive hemorrhages were also encountered. Circulatory disorders in the mucous membrane of the vocal folds are one of the signs of the inflammatory process. The absence of a granular layer in the epithelial layer and the presence of hyperchromic rod-shaped nuclei in surface cells with compacted basophilic cytoplasm indicated the development of parakeratosis.

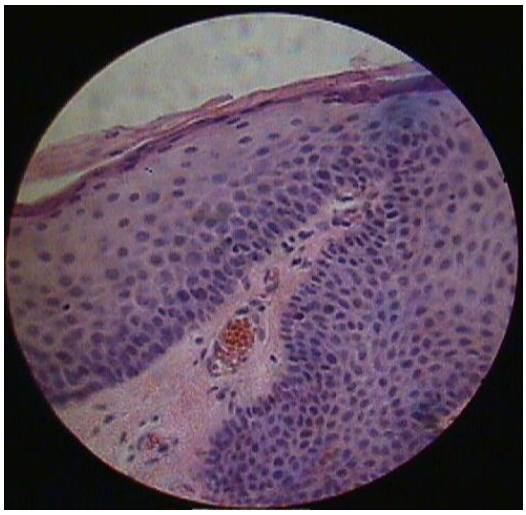

Figure 3. Proliferating epithelium, signs of its keratinization, dilated and full-blooded capillaries in the mucous membrane of the vocal folds in chronic hyperplastic laryngitis. Stained with hematoxylin and eosin. x80

A characteristic feature of the surgical material was the similarity of structural changes in the mucous membrane of the vocal folds with insufficient and excessive water. They reflected the nonspecific reaction of epithelial cells to adverse effects. The differences were mainly related to the degree of severity of these changes.

The same feature was noted in the study of the multilayer plateau of the epithelium found in smears-prints from the mucous membrane of the vocal folds. In cytological preparations, epithelial cells of the superficial elephant predominated against the background of mucus strands, bacterial flora and a small number of cellular elements of inflammation. Signs of keratinization of the epithelium at various stages, its proliferation, dystrophic and degenerative changes were revealed both with insufficient VOD and with excess. With insufficient VOD, the cells of the proliferating epithelium were combined into small layers (Fig.4), groups of 3-4 elements were created, or they were located singly. In the epithelial layers, among the unchanged cells, there were also cells with dystrophic changes, which were represented by moderate morphological rearrangements.

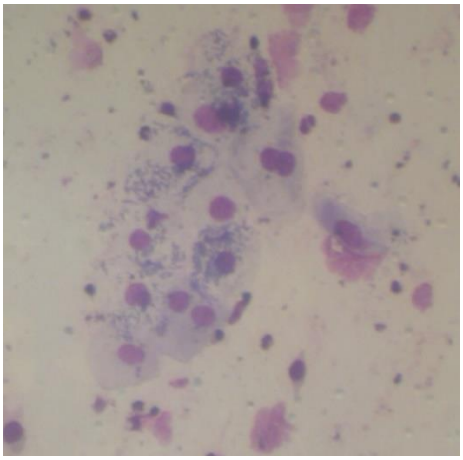

Figure 4. Conglomerate of proliferating epithelial cells in the mucous membrane of the vocal folds in chronic hyperplastic laryngitis. The May-Grunwald fixator with a Romanovsky paint job, (x400)

They consisted in reducing the stainability of the cytoplasm, lightening it, sometimes in vacuolization. In the light basophilic cytoplasm with a small number of inclusions there were hyperchromic nuclei, reduced in size, or, on the contrary, large, rounded centrally located nuclei, the cytoplasmic membrane was practically not visible, so the cell boundaries were indistinct. Epithelial cells with signs of keratinization – with a compacted granular cytoplasm and an elongated hyperchromic nucleus can also be attributed to dystrophically altered cells.

With a particular severity of the phenomena of dystrophy, degenerative changes occur in epithelial cells associated with varying degrees of cell destruction. In the studied preparations, they covered groups of cells containing different amounts of elements and manifested themselves in swelling, loss of basophilia and lightening of the cytoplasm, in which no details were distinguished, except for occasionally occurring vacuoles. The nuclei looked shrunken, hyperchromic, reduced in size, which corresponded to pycnotic changes. Some proliferates consisted of cells with signs of necrosis: the disintegration of nuclei into separate fragments (karyorexis), as well as the "melting" of the cytoplasm and the disappearance of cell boundaries. Proliferates with pronounced polymorphism of cells differing in size and shape, having a more colored cytoplasm and containing large hyperchromic nuclei were detected (Fig. 5). This allows us to judge the presence of signs of cellular atypia.

With increased vegetative reactivity and excessive VOD, the cytological picture was distinguished by the presence of a smaller number of stratified multilayer epithelial plateau, in which cells with dystrophic changes in the cytoplasm, with large, rounded, centrally located nuclei and "blurred" boundaries were located in the middle of unchanged epithelial cells (Fig. 6). Proliferates containing epithelial cells with destructive changes in the nucleus and cytoplasm, they were much less common than with insufficient VOD.

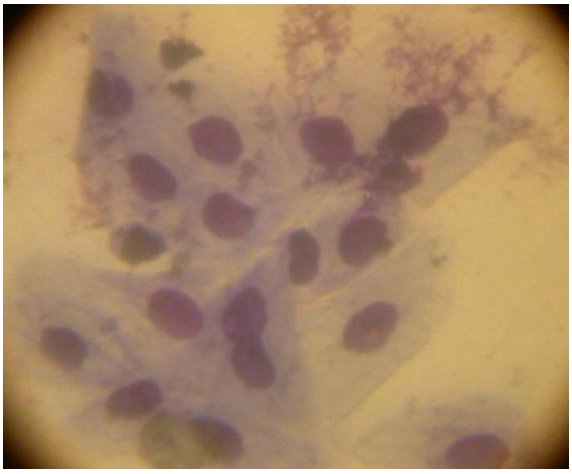

Figure 5. Polymorphism of cells of the multilayered flat non-corneating epithelium in the mucous membrane of the vocal folds in chronic hyperplastic laryngitis. The May-Grunwald fixator with a Romanovsky paint job, (x400)

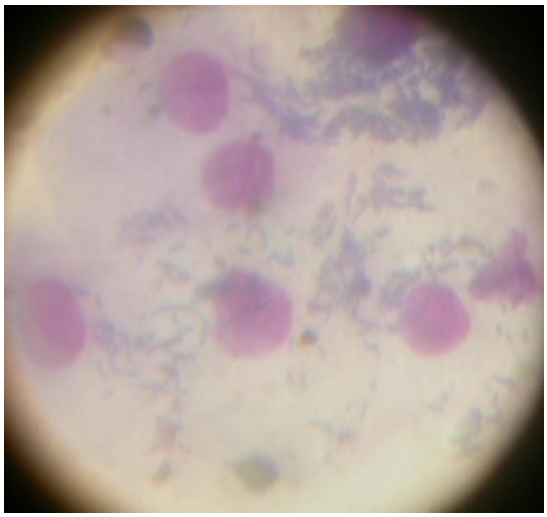

Figure 6. Epithelial cells with dystrophic changes in the cytoplasm and large centrally located nuclei in the mucous membrane of the vocal folds in chronic hyperplastic laryngitis. The May-Grunwald fixator with a Romanovsky paint job, (x900)

4. Discussion

A comparative analysis of morphological changes detected in the mucous membrane of the vocal folds showed that the proliferative activity of epithelial cells is more pronounced with insufficient VOD than with excessive. The same applies to dystrophic and degenerative changes. With excessive VOD, hemorrhages and such severe destructive changes as degeneration of the cytoplasm and the nucleus of epithelial cells, depression to necrosis, were not detected. At the same time, an additional anamnestic farrowing performed during the work process testified to the presence of a clinical picture of peripheral vegetative insufficiency in all patients [3]. Its symptoms include changes in blood pressure and heart rate, cardiac arrhythmias, chest pains, lack of air, fibromyalgia, instability when walking and fear of falling [2, 13-17]. These signs are usually not emphasized by patients and can be detected only with active and purposeful questioning.

Statistical data indicate that the IL of adrenergic interstitial nerve fibers correlates with the characteristics of VOD. At the same time, the weakened processes of synthesis, accumulation and excretion of norepinephrine from nerve fibers are associated with insufficient VOD, and the increased intensity of these processes is associated with excess. However, with increased expenditure of neurotransmitter, the intensity of its synthesis and excretion quickly reaches its maximum and further maintenance of adrenergic nerve structures in a state corresponding to excess VOD becomes impossible. Active diffusion of norepinephrine from nerve fibers and endings leads to

their emptying and contributes to the development of peripheral autonomic insufficiency and neurodystrophic changes in executive structures – targets of adrenergic innervation. Weakening of the processes of synthesis and transport of norepinephrine along vegetative fibers (insufficient VOD) or its excessive consumption (hyperreactivity and excess VOD) with subsequent deficiency of the neurotransmitter are the main neurogenic dystrophies that occur in the larynx and are accompanied by pathological changes in the ultrastructure and biochemical organization of effector cells [7]. Neurodystrophy is involved in the vicious circle of the disease in chronic hypertrophic laryngitis and becomes one of the links in its pathogenesis [1, 6, 18]. In addition, as a result of reduced resistance of the body, neurodystrophy is often the basis for the development of microbial infection. At the same time, chronic inflammation can be secondary, expanding the zones of previously arisen neurodystrophic changes, which include a variety of pathological processes: alteration, up to necrosis, atrophic and vasoparalytic disorders, disorders of proliferation and differentiation of cellular elements [19, 20]. The low content of the adrenergic neurotransmitter in sympathetic nerve fibers with insufficient VOD or its enhanced release from the granule of the content in varicose veins with excessive VOD, followed by a reduction in its reserves in innervation structures, determine the state of tension, and then depletion of the sympathetic end of the ANS up to complete "sympathectomy", when the vegetative provision of protective reactions of the body suffers [11]. In such conditions, disturbances in the regulatory activity of the ANS have a two-phase character: in the first phase, with excessive VOD, arteriole spasm develops with deterioration of blood supply to tissues, protein breakdown increases, azotemia occurs, and foci of dystrophic lesions appear in the target structures. In the second phase, there is a weakening of the vegetative regulation of recovery processes, accompanied by polyvalent hormonal insufficiency, and inflammation in both cases becomes chronic [1, 19].

5. Conclusions

Our own results correspond to the literature data and indicate changes in the functional state of the ANS in patients with chronic hyperplastic laryngitis. These changes manifest themselves at the systemic level as vegetative dystonia and vegetative dysfunction, and at the tissue level as a decrease in the activity of the peripheral adrenergic link of trophic reflection – adrenergic nerve fibers in the mucous membrane of the vocal folds. At the same time, morphological changes are detected in it, which have signs of dystrophy, and in some cases atypia, which allows us to judge the presence of conditions for the development of tumors. Long-term follow-up of the examined patients showed that in three cases there was a malignancy of chronic hyperplastic laryngitis with the formation of squamous cell carcinoma. In general, the results obtained are of great practical importance. They confirm the need to take into account the functional activity of the ANS in patients with chronic hyperplastic laryngitis and turn off measures aimed at correcting neurovegetative disorders in the treatment process.

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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

Predictors and their significance in the treatment of inflammation of the nasal cavity and paranasal sinuses of allergic etiology

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Abstract: Clinical symptoms evaluation is of great importance for an appropriate management of patients with respiratory allergy. Concomitant diseases shoud be taken in consideration before the choice of the necessary treatment options and nasal allergic inflammation pharmacotherapy. Mostly in case of nasal clinical symptoms the anatomic variations of the nasal cavity, type of sinusinflammation as well as the major nasal complaint shoud be analysed before the rational choice of treatment option. Materials and methods: 16 patients (9 males and 7 women, median age 40+13.72) with clinical symptoms of respiratory allergy were examined and divided into two groups according their sinus inflammation involvement. Nasal clinical symptoms according VAS and individual anatomy were analysed. 7 patients with allergic rhinitis without concomitant sinus inflammation were set to the first group and 9 patients with concomitant central compartment inflammation of ethmoid and maxillary sinuses were set to the second one. Individual anatomy variations and sinuses inflammation according Lund-Mackay score were evaluated by means of CT scans. Atopic state was confirmed by levels of blood sIgE with ImmunoCAP assay (Phadia). Other allergy tests included blood level of general IgE, eosinophilic cationic protein and parameters of respiratory function. Results: the group difference was supposed in case of anterior or middle nasal septal deviation with the strong correlation to central compartment maxillary and ethmoid sinuses inflammation (x2 Pearson = 0.645, p = 0.009). Also, the results supposed the group difference in symptoms of nasal obstruction. Almost all patients of group with concomitant sinus inflammation didn't present to the doctor with the major complaint of nasal obstruction (88.9%, p = 0,049). Rhinorrhea as major symptom was presented by 44.9% patients of this group. Discussion: clinical options for rational pharmacotherapy choice in patients with respiratory allergy should include nasal obstruction evaluation in case or individual anatomy and concomitant inflammation of paranasal sinuses central compartments.

Keywords: allergy, atopy, chronic rhinosinusitis, rhinitis, septal deviation.

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1. Introduction

Rational pharmacotherapy and the choice of the leading method of treatment in the case of clinical manifestations of respiratory allergy from the nasal cavity must necessarily take into account the data of a comprehensive examination and the presence of concomitant diseases and anatomical features.

For example, in the case of an otorhinolaryngological examination, it is important to analyze endoscopic examination, computed tomography to identify pathology of the paranasal sinuses and variant anatomy of the nasal cavity, which may affect tactics.

Prior to the appointment of treatment, a competent clinical assessment of the initial manifestations of rhinitis and rhinosinusitis is especially relevant.

As is known, by definition rhinitis is an inflammation of the nasal mucosa, which develops according to various data in about 40% of people [1].

Allergic rhinitis is most common among chronic rhinitis, and objective data indicate an increase in this pathology [2].

In the international classification of rhinitis by etiology, allergic, infectious and non-allergic non-infectious variants are distinguished [3].

In the case of an immune response when exposed to aeroallergen, the nasal mucosa reacts with the development of inflammation involving mast cells, CD4+ T-lymphocytes, B-lymphocytes,

macrophages, eosinophils. T-helper cells of type 2 predominate among T-lymphocytes, which are characterized by a cytokine profile with the release of IL-4, IL-5, IL-13, contributing to the production of IgE by plasma cells [1].

In the future, the interaction of IgE on the surface of mast cells of the mucous membranes with aeroallergen leads to the release of inflammatory mediators such as histamine, leukotrienes, which leads to vascular dilation, increased vascular permeability, itching, rhinorrhea, mucous discharge from the nasal cavity [2].

However, mucous discharge from the nasal cavity can also be observed in patients with pathology of the paranasal sinuses, including in the case of a chronic process.

Thus, according to the latest international classification of chronic rhinosinusitis [4], the criteria for diagnosis are the duration of the disease for more than 12 weeks and the presence of at least two complaints in the form of nasal congestion or nasal obstruction, rhinorrhea or postnasal congestion, combined with either pain or pressure in the projection of the sinuses, or with a violation of the sense of smell in adults and cough in children.

All this makes it difficult to choose the right tactics of rational pharmacotherapy in a patient with concomitant pathology of the paranasal sinuses, variant anatomy of the nasal cavity and respiratory allergies.

That is why it is important to conduct research on the analysis of leading complaints in patients with respiratory allergies and concomitant otorhinolaryngological pathology.

2. Patients and Methods

16 patients (9 men and 7 women, age 40+13.72) who were observed with clinical manifestations of respiratory allergy were divided into 2 groups depending on the available clinical features. The first group included 7 patients with allergic rhinitis, the second 9 patients with allergic rhinitis and involvement of the medial parts of the maxillary sinuses and cells of the lattice labyrinth in allergic inflammation according to computed tomography. Patients with previous surgical intervention in the nasal cavity and foreign bodies of the paranasal sinuses were excluded from the study.

The clinical diagnosis of allergic rhinitis was established in accordance with the recommendations of the RAACA on Allergic Rhinitis from 2020 and the International Conciliation Document [5]. In patients who underwent allergy testing, sensitization to aeroallergens was determined using specific IgE in the blood by ImmunoCAP (Phadia), documented data on the function of external respiration (FER).

According to the endoscopy of the nasal cavity and computed tomography of the paranasal sinuses, the indicators of involvement of the paranasal sinuses in the inflammatory process on the Lund-Mackay scale and individual variant anatomy of the nasal cavity were determined.

Complaints and their intensity were analyzed in all patients on a visual-analog scale (VAS).

Statistical processing of the results was carried out using the SPSS program, version 23.0.

3. Results

Comparison of clinical symptoms in patients in two groups showed a significant difference in the manifestations of the disease and the leading complaint from the nasal cavity. The complaint was considered the leading one with a high index on the visual-analog scale (VAS), its intensity at the initial appeal was 8 + 0.79 points. In patients of the first group with isolated allergic rhinitis, nasal congestion prevailed (in 4 patients out of 7, 57; 14%) and nasal discharge or rhinorrhea (in 3 out of 7 patients; 42.86%).

In the majority of patients of the second group (8 out of 9 patients; 88.9%), it was not obstructive syndrome and nasal congestion that prevailed, but complaints such as mucous discharge from the nose and rhinorrhea (44.4%), sneezing (11.11%), lacrimation (11.1%), dryness (11.1%), pain in the forehead (11.1%). Only one patient out of 9 with respiratory allergies and involvement of the central parts of the maxillary sinuses and the cells of the lattice labyrinth in the inflammatory process and concomitant curvature of the septum, nasal congestion was the leading complaint.

Taking into account the analysis of the variant anatomy of the nasal cavity and paranasal sinuses in patients of two groups, it was revealed that in the group of patients with involvement of the paranasal sinuses in the inflammatory process, such changes in individual anatomy as curvature of the nasal septum in the anterior/middle sections occurred in 9 out of 9 patients, in 100% of cases, unlike the first group where such changes were observed in 3 out of 7 patients (in 42.86%), the difference between the groups was statistically significant ($p = 0.009$).

In the group of patients with isolated allergic rhinitis, where the leading complaint of obstructive syndrome was more common, there was also a curvature of the nasal septum in the posterior parts (in 3 out of 7 people (42.86%), which distinguished it from the second group, where curvature in the posterior parts was not noted, the difference between the groups for this parameter was statistically significant ($p = 0.029$).

Data were also obtained that in the second group of patients with inflammatory changes in the central parts of the nasal cavity and paranasal sinuses, in contrast to patients of the first group with isolated allergic rhinitis, there were such changes in variant anatomy as infraorbital cells or Haller cells (in 4 patients out of 9, 44.4%), the difference between the groups was statistically significant (p=0.042).

The frequency of development of such a leading complaint as nasal congestion and changes in variant anatomy in two groups is shown in figure 1.

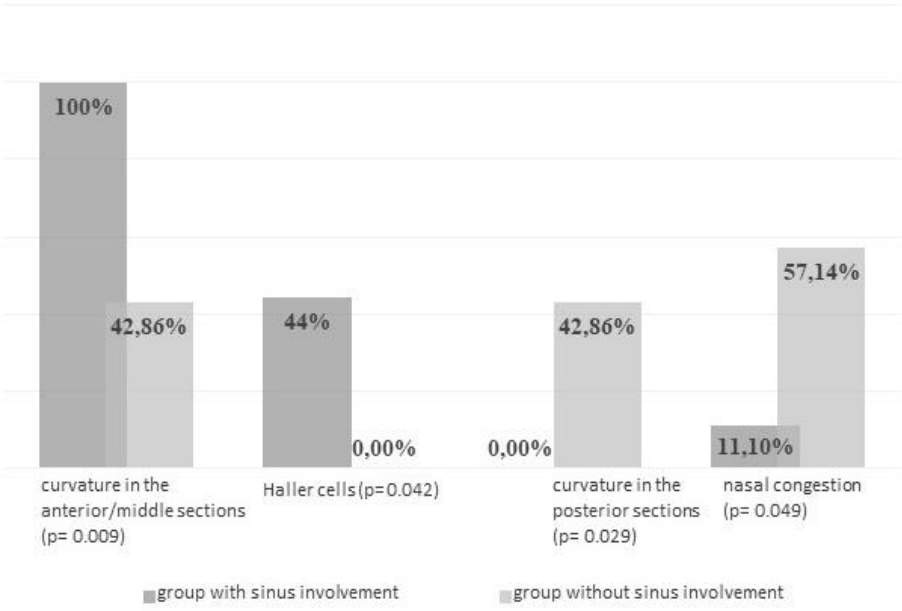

Figure 1. The difference between the groups according to the variant anatomy of the nasal cavity and the leading complaint in the form of nasal congestion.

In two groups of patients with both isolated allergic rhinitis and allergic rhinitis and involvement in the inflammatory process of the medial parts of the paranasal sinuses, there was no such comorbid pathology as bronchial asthma according to the assessment of respiratory function.

4. Discussion

A variant of central inflammation of the maxillary sinuses and the cells of the lattice labyrinth in chronic rhinosinusitis is known and included in the international classification of 2020 as atopic disease of the central parts of the nose [Grayson].

Taking into account the terminology of "atopic disease", it is important to analyze complaints, their similarity and difference from complaints of patients with allergic rhinitis, since at the moment it is known that 100% of patients with this nosology have respiratory allergies [6].

According to our study, in some patients with respiratory allergies, concomitant inflammation was indeed detected mainly in the medial parts of the maxillary sinuses and the cells of the lattice labyrinth. An example of computed tomography of a patient in a coronary projection is shown in Figure 2.

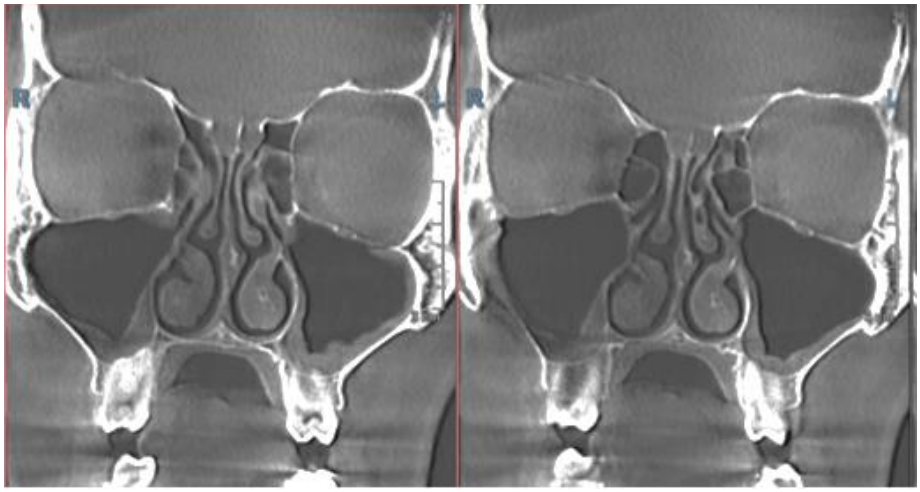

Figure 2. Involvement of the paranasal sinuses in the process of inflammation in respiratory allergies.

And such patients with involvement in the inflammatory process of the sinuses did not have such a comorbid pathology as bronchial asthma, which corresponds to the data described by foreign colleagues [6].

However, in the case of a decision on the primary conduct of rational pharmacotherapy and allergen-specific immunotherapy and surgical intervention, it is necessary to evaluate the leading complaints of the patient.

In our case, the majority of patients with respiratory allergies and concomitant involvement of the paranasal sinuses in the process of inflammation (89.9%) did not have symptoms of nasal congestion and obstructive syndrome, despite the presence of a curvature of the nasal septum in 9 patients out of 9 (in 100% of cases), which corresponds to the clinical diagnosis of a curvature of the nasal septum without respiratory dysfunction, and if the patient's management tactics are chosen, it indicates more in favor of primary rational pharmacotherapy of respiratory allergy, supplemented with allergen-specific immunotherapy, with the subsequent fortification of ASIT by supplementing with endoscopic rhinosurgery and/or septoplasty.

5. Conclusions

The data obtained by us indicate the importance of the syndromic approach and assessment of the leading complaint when choosing the primary management tactics of a patient with respiratory allergies, which is especially necessary in the case of concomitant pathology in the form of variant anatomy of the nasal cavity and involvement in the process of inflammation of the paranasal sinuses.

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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

Clinical application of photobiomodulation therapy to reduce the severity of acute pain after septoplasty

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Abstract: The purpose of the study: to evaluate the effectiveness of photobiomodulation (PBM) in the early postoperative period after septoplasty. Materials and methods: 62 patients have undergone septoplasty under general anaesthesia. Among them, there were 40 men and 22 women from 18 to 44 years of age. After septoplasty, the nasal cavity was tamponaded with foam tampons in glove rubber. The patients were divided into two groups of 31 participants, with the equal number of men and women in each of them. Patients of group 2 underwent PBM in 3 hours, 6 hours and 24 hours after septoplasty. The emitter heads generated infrared pulsed laser radiation of 0.890 microns wavelength and the power of 10 W. The emitter heads were installed for 2 minutes in the projection of the lateral cartilage and large cartilage of the nasal wing on both sides. In 48 hours after the operation, nasal swabs were removed in patients of both groups. In group 2, intranasal PBM therapy with a nozzle was performed in the continuous, modulated mode of operation in the red optical range, with the wavelength of 0.63 microns and radiation power of 8 mV for 2 minutes. Ultra-low frequency (ULF), hight frequency (HF), low frequency (LF), and total heart rate variability (HRV) power were evaluated, as well as the pain syndrome. Results. ULF was significantly lower in group 2 (8086±3003 msec^2), compared to group 1 (18580±2067 msec^2) ($p<0.001$). LF was significantly higher in group 1 (1871±405 msec^2), compared to group 2 (1095±190 msec^2) ($p<0.005$). In group 2, HF was lower – 1157±220 msec^2 versus 1630±263

msec^2 in group 1 ($p<0.01$). In group 2, the total HRV power was also lower (13498±3226 msec^2) than in group 1 (26808±2371 msec^2) ($p<0.001$). In the first three hours after the septoplasty, pain intensity did not differ between the groups. In group 2, pain decrease was observed after 6 hours, compared to the previous period ($p<0.05$). The pain continued to decrease in both groups, and 48 hours after septoplasty, patients either did not feel pain, or it was minimal and did not cause obvious discomfort. At the same time, in the period from 6 to 24 hours after septoplasty, patients who did not undergo PBM experienced significantly higher pain syndrome than patients with PBM ($p<0.001$). Conclusion. The use of PBM therapy with nasal tamponade after septoplasty helps to reduce pain severity as well as an inflammatory response to the surgical stress and, consequently, leads to less pronounced changes in the autonomic nervous system in response to the surgery.

Keywords: septoplasty, pain, photobiomodulation, heart rate variability.

1. Introduction

Surgical correction of the curved nasal septum (CNS), or septoplasty, is one of the most common rhinosurgical operations. Nosebleeds, nasal septum hematoma, acute rhinosinusitis and pain syndrome are considered the most frequent complications after septoplasty [1, 2]. Septoplasty consists of the muco-suprachondral and/or muco-periosteal leaves separation and curved areas of the cartilaginous and/or bony parts of the nasal septum removal. As a rule, smooth sections of the extracted cartilaginous part of the nasal septum are placed back between the two leaves of the epiglottis. At the same time, the nasal cavity is tamponed after surgery to avoid complications [3].

The issue of patients' rehabilitation after septoplasty remains of essential importance. This may include both the question of anaesthesia and analgesia therapy quality, and the choice of local medicines application. For example, it was previously demonstrated that septoplasty by itself [4], as well as low-quality anaesthesia, may provoke the development of distress syndrome, which is an imbalance of the autonomic nervous system, severe pain syndrome and failure of life quality in the early postoperative period, which is confirmed by both changes in the balance of the autonomic nervous system (ANS) and changes in heart rate variability (HRV) [5].

Nowadays to reduce the appearance of side effects after septoplasty, such as pain, tissue oedema, inflammation, ecchymosis, etc, photobiostimulation (PBM) has been increasingly used [6]. This technique is based on the accelerating tissue repair principle, and therefore, the surgical wound healing [7, 8]. PBM therapy is a form of low-intensity laser therapy. PBM uses non-ionizing light sources, such as lasers or light-emitting diodes with a wavelengths 600-1000 nm and power less than 500 MW [9], to induce a photochemical reaction that leads to increase ATP synthesis in mitochondria, signal transmission in biological membranes and cells, DNA synthesis, cell proliferation, differentiation, and modulation of pro-and anti-inflammatory mediators, and, as a consequence, a reduction in pain and inflammation [10-12]. PBM is widely used to treat various diseases and conditions, such as wounds, diabetic ulcers, pain, inflammation, blood diseases, musculoskeletal complications, coronary heart disease, tissue repair and regeneration [13-14].

In nasal surgery, the problem of the postoperative quality of life of patients occupies a special place [15]. In addition to pain, nasal cavity tamponade presents significant inconveniences for patients. At the same time, there is an opinion that after septoplasty, instead of tamponade, splines should be used [15]. However, both tamponade and splints have their own advantages and disadvantages [5]. It seems interesting to search for non-invasive methods of rehabilitation of patients after septoplasty with nasal cavity tamponade. Resolving this issue will likely shorten the period of nasal cavity tamponade after septoplasty and improve the quality of life of patients.

The literature review shows that after septoplasty, PBM is applied intranasally after the removal of tampons, or immediately in the case of splints [15]. At the same time, there are practically no data on the evaluation of PBM effectiveness, when exposed during tamponade in the first two days after septoplasty.

Considering all of the above, this study was conducted to evaluate the effectiveness of PBM therapy in the early postoperative period in patients after septoplasty.

2. Patients and Methods

2.1. Rhinosurgery.

The study was approved by the Ethics Committees of the RUDN University Medical Institute. 62 patients have undergone septoplasty under general anesthesia. 40 men and 22 women from 18 to 44 years of age were included in the study. The participants were randomly assigned to two

groups of 31 patients each, with the equal number of men and women in both groups. The women underwent septoplasty during the periovulatory period. This phase of the ovarian-menstrual cycle is known to have a lower risk of nosebleeds after rhinosurgery [16]. Immediately after the operation, all the patients received anterior nasal tamponade with gauze swabs in glove rubber for 2 days. All the patients underwent septoplasty using local infiltration anesthesia with 1% procaine solution (250 mg) along with 0.1% epinephrine solution (10 mg) and general anesthesia using fentanyl (30 mkg/ml), propofol (150 mg), cisatracurium bezilate (nimbex) (6 mg), tranexamic acid (tranexam) (1000 mg), atropine (0.5 mg) and metoclopramide (cerucal) (10 mg). To avoid the development of acute bacterial inflammation of the paranasal sinuses, oral antibacterial therapy of azithromycin 500 mg once in the morning for three days with the first dose in the morning on the day of surgery was prescribed.

Exclusion criteria from the study were age less than 18 years, cardiovascular diseases, diabetes, endocrinological diseases, kidney diseases, oncological diseases, mental disorders, menstrual disorders and gynecological diseases, bronchial asthma, chronic hepatitis, chronic diseases of the gastrointestinal tract.

2.2. PBM therapy.

3 hours, 6 hours, and 24 hours after the septoplasty, group 2 patients received PBM therapy. The emitter heads generated infrared pulsed laser radiation with a wavelength of 0.890 microns and a power of 10 W. The emitter heads were placed in the projection of the lateral cartilage and the prominent cartilage of the nasal wing on both sides for 2 minutes.

48 hours after the operation, nasal swabs were removed in patients of both groups, and in group 2, intranasal PBM therapy with a nozzle was performed in the continuous, modulated mode of operation in the red optical range, with the wavelength of 0.63 microns and radiation power of 8 mV. The emitter heads were placed in both halves of the nose for 2 minutes.

2.3. HRV and pain syndrome analysis.

To assess the HRV, daily Holter electrocardiogram (ECG) was recorded using MT-200 devices (Schiller, Swiss). The ECG recording system was installed in patients 30 minutes before the septoplasty and removed 24 hours after it. The HRV parameters were studied in the frequency range: low frequencies (LF) in $msec^2$, ultra-low frequencies (ULF) in $mcec^2$, high frequencies (HF) in $msec^2$ and total power (Total power) in $msec^2$.

Pain syndrome was assessed using a visual-analogue scale (Fig. 1) at 1, 3, 6, 12, 24 and 48 hours after septoplasty and in group 2 immediately after PBM therapy sessions. The patients were asked to place a vertical line or dot at a point on the scale that they thought corresponded to the pain they were experiencing. The scale length was 100 mm. The pain intensity was measured in mm.

Figure 1. Visual-analogue scale for assessing the intensity of acute pain syndrome.

2.4. Statistical analysis.

All statistical data processing was performed using the JASP software package, version 0.14.0 (the University of Amsterdam, Netherlands) for Windows ®. Continuous variables (pain value, LF, ULF, HF, Total power) were presented as mean±error of mean and analyzed using the t-test of independent samples after checking normality using the Shapiro-Wilk test. Normally distributed data were evaluated using the Student's t-test of independent samples, and abnormally distributed data were assessed using the Mann-Whitney's U-test. The values of $p<0.05$ were considered statistically significant.

3. Results

3.1. Heart rate variability.

Student's t-test showed that after the sessions of PBM therapy, the ultra-low-frequency component of HRV spectral analysis was significantly lower in group 2 (8086±3003 $msec^2$), compared to group 1 (18580 ± 2067 $msec^2$) ($p<0.001$) (Fig. 2a). The low-frequency component of HRV was significantly higher in group 1 (1871 ± 405 $msec^2$), compared to group 2 (1095 ± 190 $msec^2$) ($p<0.005$), which indicates an increase in the sympathetic tension of the ANS in the group without

FBMT (Student's t-test) (Fig. 2b). According to the Mann-Whitney U-test based on the high-frequency component of HRV analysis, a decrease in the activity of the parasympathetic nervous system during the perioperative day was also recorded in group 2 as a whole – 1157 ± 220 msec^2 versus 1630 ± 263 msecec^2 in the first group ($p<0.01$) (Fig. 2c). In group 2, the total HRV power was significantly lower (13498 ± 3226 msec^2) than in group 1 (26808 ± 2371 msec^2) ($p<0.001$) (Student's t-test) (Figure 2d).

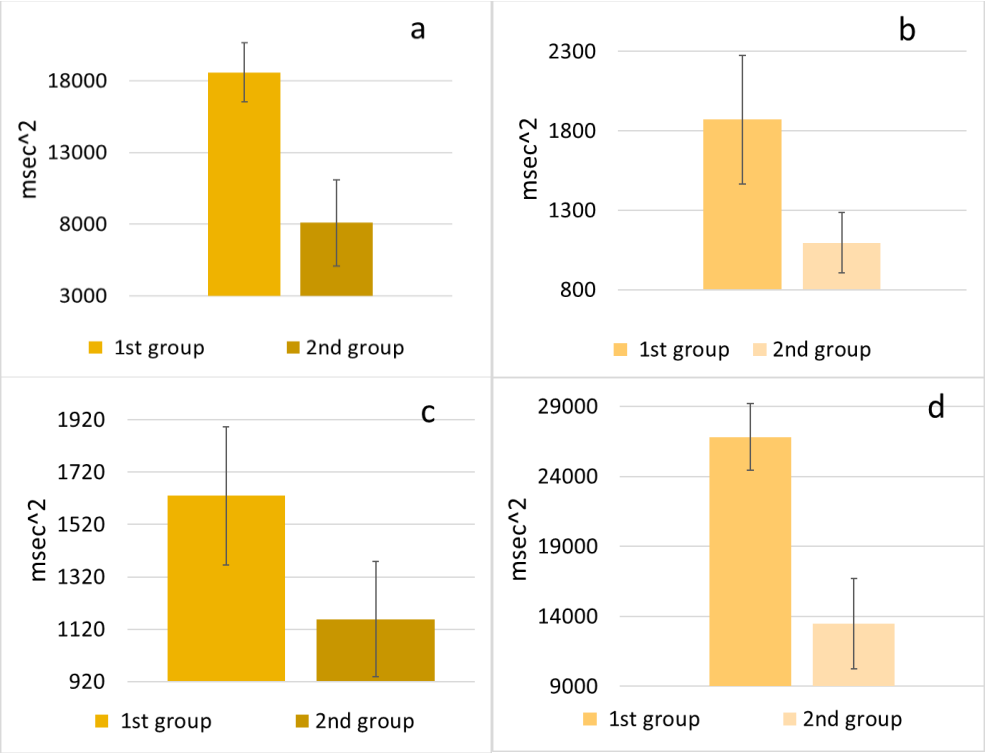

Figure 2. Changes in the frequency of heart rate variability with the use of PBMT after septoplasty and without it: a-ULF, b-LF, c-HF, d-Total power. The error bars indicate standard error.

3.2. Pain syndrome.

In the first three hours after the surgical intervention, the intensity of pain severity did not differ between the groups. The Mann-Whitney U-test showed that in group 1, the intensity of pain increased after 6 hours, compared to 3 hours after surgery, but there was no significant difference recorded. In group 2, the intensity of pain syndrome began to decrease after 6 hours, compared to the previous period ($p<0.05$) (Mann-Whitney U-test) (Fig. 3). Further, the pain syndrome continued to decline in both groups, and 48 hours after the septoplasty, the patients either did not feel pain, or it was minimal and did not cause pronounced discomfort. At the same time, in the period from 6 to 24 hours after surgery, the patients who did not undergo PBMT experienced significantly higher pain syndrome than the patients with PBMT ($p<0.001$) (Mann-Whitney U-test) (Fig. 3, Table 1).

Table 1. Intensity of acute pain syndrome after septoplasty.

Time after surgery	1 hour, mm	3 hours, mm	6 hours, mm	12 hours, mm	1st days, mm	2nd days, mm
Group 1	17.15±2.46	21.82±2.83	25±2.02	21.64±2.36	16.68±1.01	3.68±1.01
Group 2	14.16±2.31	18.88±2.45	16.43±2.08	12.83±2.38	10.84±1.15	3.84±1.15

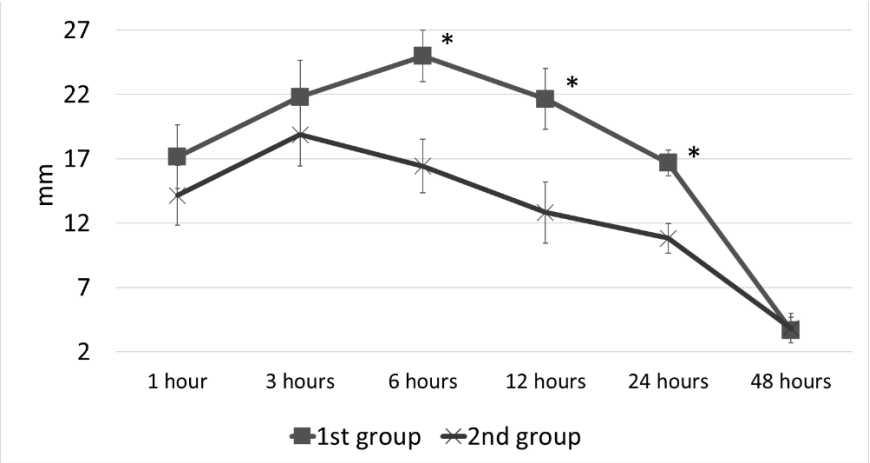

Figure 3. The intensity of pain syndrome after septoplasty. * - significant differences between the groups at p<0.001. The error bars indicates standard error.

4. Discussion

The presented study is one of the few that shows the effectiveness of the use of PBMT in patients with nasal cavity tamponade in the first two days after septoplasty.

It is known that the removal of tampons is advisable 2 days after surgery, when there is a decrease in inflammatory processes with simultaneous restoration of the mucous membrane, normalization of blood supply to cartilaginous and bone tissues [1, 2], so it becomes relevant to use PBM therapy during the first two days after surgery. To date, it has not been found in the literature that PBM therapy is carried out with intranasal swabs with a high frequency of therapy sessions on the first day after rhinosurgical interventions in patients after septoplasty.

It is generally assumed that the PBM biological effect mechanism implies the absorption of light by chromophores [17, 18]. PBM therapy results in the following effects: reduction of oedema and inflammation, reduction of pain, collagen synthesis, increased elasticity, increased tissue perfusion and increased tissue vascularization, increased cell proliferation, especially fibroblasts, which generally leads to the restoration of damaged tissues [6]. Recent studies have shown the effectiveness of PBM therapy in a variety of conditions, from diabetic foot to androgenetic alopecia and post-chemotherapy mucositis, as well as wound healing and inflammation reduction [7, 8, 17 - 19]. PBM therapy may play a role in reducing the number of new postoperative haemorrhages in the maxillofacial region. At the same time, PBMT is positioned as a unique alternative to other interventions since it is an easy-to-use and minimally invasive method [6].

Hersant et al. evaluated the effect of low-intensity laser on flap survival results in facial plastic surgery. The authors showed that PBM therapy increases flap survival as well as wound healing. However, some possible effects of skin ageing were reported [20]. Enwemeka et al. found highly efficient tissues restoration promoted by PBMT during all three phases and pain reduction [21].

The effects of PBM therapy described above, significantly damaged tissues restoration and neovascularization, provide edema and inflammatory reaction reactions, a reduction in haemorrhage likelihood [6] and, consequently, pain in the tissue after septoplasty. With the intranasal use of PBM therapy, systemic effects are also achieved through blood cells and components [22], which probably can contribute to a positive neurotherapeutic impact [23]. The tissues adjust to the nasal cavity have an abundant blood supply with relatively slow blood flow. PBMT has shown to improve blood rheology [24], reduce blood viscosity [25], and enhance blood clotting status [26, 27] in various pathological conditions. In group 2, significantly lower intensity of pain syndrome, a decrease in its power compared to patients of group 1, indicates relatively low inflammatory reactions of the blood system in the damaged area after PBMT [28].

In patients with PBM therapy, HRV indicators had significantly lower total power than those without PBM therapy, for example, an ULF component often associated with circadian rhythms [29]. An increase in ULF power indicates a failure of circulatory rhythms due to surgical traumatization against the background of inflammatory phenomena in the group without PBM therapy. The high-frequency component of HRV shows the parasympathetic nervous system tonus, while LF, according to a number of authors, can reflect both sympathetic (mainly) and parasympathetic one [30]. The decrease in LF and HF after septoplasty with the use of PBM therapy demonstrates the reduction in sympathetic and parasympathetic tonus after the correction of CNS. The shift in the balance of the ANS towards its sympathetic component is physiologically justified and corresponds to the severity of the stress factors impact. However, an increase in the tonus of the parasympathetic nervous system under stress may indicate an inadequate response of the body and

correspond to distress syndrome [31], which may reflect the degree of surgical damage in the maxillofacial region [32]. Thus, it was shown that after septoplasty, LF of HRV could sharply decrease [30]. In our study, a group of patients with the classic variant of postoperative rehabilitation had increased activity of both the sympathetic and parasympathetic parts of the ANS. Studies have shown a relationship between blood rheology, cognitive function [28], and mood improvement [27]. It has been suggested that the systemic effects of PBM therapy after blood irradiation may also ultimately have a neuroprotective effect [23, 33, 34]. Intranasal blood irradiation is also known to have the same neurological consequences as intravenous or intravascular PBM therapy [35]. Those findings may also provide insight into lower pain syndrome, lower changes in the ANS balance in response to surgical damage after septoplasty in patients with photobiomodulation in the early postoperative period.

5. Conclusions

To sum up, in our study, the group of patients with PBM therapy showed better results regarding pain syndrome decrease and HRV compared to the classical patients' rehabilitation after septoplasty. In our opinion, it is necessary to further develop protocols for the patients' rehabilitation after septoplasty with various types of nasal tamponade.

It is likely that the use of PBMT in the future can serve as one of the ways to reduce the duration of nasal tamponade after septoplasty as a result of accelerating the reparative processes of the nasal septum mucosa. Thus, we will be able to approach solving the problem of the quality of life of patients in the early postoperative period after nasal septum surgery with the nasal tamponade use.

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Article

Preclinical studies of natural astaxanthin in laboratory animals.

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Abstract: This article discusses the issue of finding new dental drugs that have antibacterial, anti-inflammatory, wound healing, immunomodulatory effects and exhibit minimal side effects to avoid complications from internal organs.

Keywords: antioxidant gel, astaxanthin, interferon, acute and chronic toxicity, local irritant effect, preclinical studies.

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1. Introduction

The search for new promising dental products with anti-inflammatory, wound healing, antibacterial and immunomodulatory effects and thus showing minimal side effects is a rather urgent task of modern scientific and practical medicine. Astaxanthin is a natural antioxidant that is present in various quantities in living organisms and belongs to the class of carotenoids by its chemical structure.

Another active ingredient of dental gel is interferon alpha, which has the ability to stimulate phagocytic activity of macrophages and cytotoxic activity of T-cells and NK-cells. It has an indirect antiviral effect, increasing the body's resistance to viral infections and modulating the immune system response aimed at neutralizing viruses or destroying cells infected by them.

2. Patients and Methods

Antioxidant gel with interferon was studied in young outbred rats.

3. Results

According to the results of the experimental study there were no changes in the clinical and biochemical analysis of peripheral blood in both experimental and control groups of animals. No significant changes in the behavior and motor activity of the animals of the experimental groups were observed after 30-day administration of the gel. Rectal temperature measurement data demonstrate that in animals of both the experimental and control groups the body temperature did not differ from normal. No signs of local inflammatory reaction were registered during application of the studied gel to the mucous membranes of the oral cavity.

4. Conclusion.

In the study of toxicity and possible local irritant effects no complications in the internal organs and no local inflammatory reaction were registered, as evidenced by the results of experimental studies.

5. Authors' Contributions.

Currently, the problem of development and introduction into dental practice of modern, effective and safe in the use of medicines based on active pharmaceutical substances of domestic origin is a rather pressing problem of medical science and practice.

When creating a dental gel with antiviral and anti-inflammatory properties, it was decided to use astaxanthin and interferon-alpha as the main active substances.

Astaxanthin is a carotenoid belonging to the group of xanthophylls. The chemical structure of this compound provides it with a pronounced antioxidant activity that makes it stand out among other natural antioxidants [1]. At present astaxanthin is successfully used in medical practice [2].

Another active ingredient of the dental gel is interferon alfa. It has the ability to stimulate the phagocytic activity of macrophages as well as the cytotoxic activity of T cells and NK cells, has an indirect antiviral effect, increasing resistance to viral infections and modulating the immune system response to neutralize viruses or destroy cells infected by them [9,10].

Currently, the urgent task of medicine is to develop domestic remedies that not only have antiviral effect, anti-inflammatory, wound healing, antibacterial and immunomodulatory properties, but also have no side effects, as well as not causing addiction [11].

This study aims to establish the toxic, maximum tolerated and lethal doses of the developed dental gel and to study its effect on the main systems and functions of the body when administered intragastrically (in a single injection) and when applied locally (in a chronic toxicity study) in the studied doses to mature animals compared with placebo in accordance with the existing requirements.

The study is part of the complex of preclinical studies of the developed drug.

6. Purpose of work.

To carry out toxicity studies on laboratory animals of a dental gel (Astadent, gel for external use 2.6 % with interferon) containing natural astaxanthin and interferon alpha as active pharmaceutical substances.

7. Materials and methods.

The object of the study was the developed Astadent gel containing natural astaxanthin and interferon alpha as active pharmaceutical substances.

Determination of acute toxicity was performed on outbred mice (males, 66 animals) with a single injection of 500 mg/kg. Clinical signs of intoxication (lethargy, ruffling, stunned, shortened breathing, salivation) were revealed.

The study drug was administered intragastrically with a special probe in increasing doses. Dosing was carried out based on the content of the active substances. The follow-up period was 14 days.

During the entire experimental period, each animal was observed twice a day: in the morning and in the afternoon. On the day of drug administration, the animals were observed every hour. The results of the examinations were recorded in laboratory charts.

Assessment of the toxic effect of Astadent gel was carried out according to the following clinical signs:

- number and timing of animal death (if any);
- respiratory indicators (labored breathing, cyanosis, rapid breathing, nasal discharge);
- motor activity (elevated/reduced, somnolence, loss of balance, sensitivity, catalepsy, ataxia, unusual movements, prostration, tremor, fasciation);
- convulsions (clonic, tonic, tonic-clonic, asphyxial);

reflexes (corneal, equilibrium, myotactic, light, fright reflex);

-eye signs (lacrimation, miosis, mydriasis, exophthalmus, ptosis, clouding, iritis, conjunctivitis, chromodactria, weakening of the blinking membrane);

-high salivation;

-condition of hair coat (piloleiomyoma, alopecia);

-muscle tone (hypotension, hypertension);

- indicators of the gastrointestinal tract (soft stool, diarrhea, vomiting, polyuria);

-dynamics of body weight;

-macroscopic examination of organs and tissues;

-morphometric evaluation of organs (heart, thymus, liver, kidneys, adrenal glands, lungs, spleen, testes, ovaries).

To assess chronic toxicity, the drug was applied to the gingiva for 30 days. The surface of the treated mucosa was approximately 0.5x0.5 cm. In this regard, it was decided to use 2 doses when the drug was repeatedly applied:

- 43 mg/kg - approximately 10 times the maximum daily dose for humans per rat -8.6 mg/rat.

- 86 mg/kg - about 100 times the maximum human daily dose per rat - 17.2 mg/rat.

The dose of interferon was 106 IU -14286 IU/kg.

The studies were performed on young male outbred rats, which were randomly allocated groups (5 animals in each group, males/females). The first group received prophylactic gel for 30 days at a dosage of 43 mg/kg animal weight, the second group received 86 mg/kg, the third group being the control did not receive Astadent gel. The initial criterion was the body weight of the animal, which was 180-200 g.

In the subchronic experiment, animals were observed once a day, immediately before the application of the drug, to detect deviations in health status and mortality. The appearance of the animals in the cage, the behavior of each, the state of feces, etc., were examined. Animal body weight was determined weekly before administration of the study drug. Feed and water consumption were recorded daily.

Thirty days after drug administration all animals of the group (preliminarily deprived of food for the night) had biochemical and clinical blood parameters determined. Blood sampling was performed from the tail vein.

To determine clinical parameters, blood was placed in 0.9 ml tubes with EDTA and tested on an automatic hematology analyzer PCE 90 VETHTI, ERMA (Japan) to determine the number of erythrocytes, leukocytes, thrombocytes, hemoglobin level, hematocrit, etc.

To assess biochemical parameters, blood was collected in 1.0-2.0 ml tubes without anticoagulant, centrifuged to obtain serum, in which the following parameters were determined on automatic biochemical blood analyzer ILAB 650 (USA) using kits from "Biosistems", Spain: total protein, albumin, total cholesterol, triglycerides, total bilirubin, glucose, urea, creatinine, alkaline phosphatase activity, alanine and aspartataminotransferase.

8. Statistical analysis.

After completing the experimental studies, statistical processing of the results was carried out by the method of variation statistics using Student's t-criterion. Statistical data were processed using Microsoft Office Excel.

9. Results and discussion.

9.1. Clinical observations.

Application of Astadent in animals for 30 days at a dose of 43 mg/kg and 86 mg/kg, respectively, did not cause changes in the main integral indices in rats.

The animals were active and had a neat appearance. The consumption of dry feed and water by the rats of the experimental groups corresponded to the control parameters. During the subchronic experiment, no animal death was observed in any of the experimental groups.

9.2 Effect on body weight, feed and water consumption

During the experiment, the test animals were monitored, recording the change in body weight weekly. The dynamics of weight changes for female and male rats for 30 days are shown in Table 1 & Table 2.

Table 1. Change in body weight in white male rats during the course of application of "Astadent" gel.

Drug, dose	Changes in the body weight of animals as a % of the initial through:			
	1 day		30 days	
	m	Sr	m	Sr
Control	119,5	5,0	119,2	5,4
Test drug "Astadent"				
43 mg/kg	121,2	4,1	121,5	4,1
86 mg/kg	122,5	3,1	122,1	4,1

Table 2. Change in body weight in female white rats during the course of application of "Astadent" gel:

Drug, dose	Changes in the body weight of animals as a % of the initial through:			
	1 day		30 days	
	m	Sr	m	Sr
Control	116,5	4,1	120,6	3,1
Test drug "Astadent"				
43 mg/kg	119,4	3,2	119,5	4,1
86 mg/kg	119,8	4,0	119,5	4,1

In the groups that received Astadent dental gel in both doses, the body weight gain did not differ from the weight gain of control animals.

The daily feed and water consumption was counted weekly. The amount of feed and water consumption by the rats receiving the above preparations did not statistically differ from the parameters of the animals in the control groups (Table 3).

Table 3. Daily water and feed intake in white rats after application of «Astadent» gel:

Drug, dose	Males				Females			
	Dry feed intake, g /100 g		Water consumption, ml /100 g		Dry feed intake, g /100 g		Water consumption, ml /100 g	
	m	Sr	m	Sr	m	Sr	m	Sr
Control	8,54	1,30	8,30	1,30	6,40	1,20	7,20	1,37
Test drug "Astadent"								
43 mg/kg	9,15	1,10	9,70	1,10	6,25	1,70	9,10	1,30
86 mg/kg	9,10	1,20	9,50	1,19	7,55	2,00	9,10	1,20

9.3 Effect on animal body temperature:

The body temperature of the animals was measured rectally. The state of these vital signs of the body was studied in accordance with the Protocol at the beginning and 30 days after the beginning of the application. The results of measuring the rectal temperature of the rats (5 animals of each sex from the experimental groups) using an electric medical thermometer TPM - 1 (permissible basic error from the range of measured temperatures, % ± 1) are presented in Table 4.

Table 4. Effect of astadent gel on the rectal temperature of white rats (oC, Mm)

Timing of the study	"Astadent», mg			
	Control		86 mg/kg	
	M	F	M	F
Background	34.1±0.2	35.2±0.1	35.1±0.2	35.1±0.2
30 days	35.2±0.2	35.3±0.1	35.1±0.2	35.3±0.2

Rectal temperature measurement data demonstrate that in the animals of the experimental groups, as well as in the control group, the body temperature did not differ from the baseline data.

9.4 Influence on parameters of functional state of kidneys.

Condition of excretory system - kidneys was determined after water load, which was 2.5 % of "starvation" body weight. Eighteen hours before the experiment the animals were deprived of

food, leaving free access to water, consistently for four hours the animals were placed in exchange chambers to collect urine. The volume of excreted urine was measured, diuresis per 100 g of each animal's weight was calculated, and the relative density of urine was determined (Table 4 & Table 5)

Table 4. Urine parameters of male rats when using «Astadent» gel

Drug, dose	Urine volume / relative urine density	Presence of pathological elements in the urine
Control	1,71/6,40	-
Test drug "Astadent"		
43 mg/kg	1,75/6,3	-
86 mg/kg	1,77/7,2	-

Table 5. Urine parameters of female rats when using «Astadent» gel

Drug, dose	Urine volume / relative urine density	Presence of pathological elements in the urine
Control	1,72/6,1	-
Test drug "Astadent"		
43 mg/kg	1,74/6,2	-
86 mg/kg	1,75/6,1	-

9.5 Effect on motor and exploratory activity.

Experiments were performed on 5 rats of each sex from each experimental group. The rats were placed one by one in the "open field" system, where their movements were recorded for 35 minutes. Table 6 & Table 7 presents the data on the effect of astadent gel on the spontaneous motor activity (SDA) of the rats.

Table 6. Effect of astadent gel on motor activity of rats of white rats (male)

Drug, dose	Number of crossed squares		Number of stand ups		Number of peeks into the holes
Control	9,3		3,2		8,2
Test drug "Astadent"					
43 mg/kg	10,3	1	3,0	1	8,0
86 mg/kg	9,2	1	3,1	1	8,1

Table 7. Effect of astadent gel on motor activity of rats of white rats (females)

Drug, dose	Number of crossed squares		Number of stand ups		Number of peeks into the holes
Control	10,2		3,1		8,1
Test drug "Astadent"					
43 mg/kg	10,2		3,2		8,2
86 mg/kg	10,3		3,2		8,1

The data given in the tables indicate that there were no significant changes in the structure of behavior and motor activity of the animals of the experimental groups after 30 days of gel administration. A change in the behavioral pattern, characteristic of the animals secondary placed in the "open field" experiment, was noted, mainly due to the lengthening of the latent period, which was also of an unreliable nature.

9.6 Effect on peripheral blood parameters.

Peripheral blood parameters in animals treated with astadent gel are presented in Table 8 & Table 9.

Table 8. Effect of the test Astadent gel on the composition of peripheral blood in male white rats, (M ±m) (after 30 days)

The studied indicators	Control	"Astadent" 43 mg/kg	"Astadent" 86 mg/kg
Leukocytes, *10^9/l	7,8±0,1	7,5±0,1	8,2±0,1
Erythrocytes,*10^{12}/ l	5,8±0,1	6,9±0,1	6,4±0,1
Hemoglobin, g/ l	137,0±0,1	125,5±0,2	140,0±0,1
Hematocrit, %	33,0±0,2	38,8±0,2	35,4±0,2
MCV, Fl.	50,0±0,1	45,0±0,2	47,8±0,2
MCH, picograms	21,0±0,1	20,0±0,1	19,0±0,1
MCHC, g/l	30,0±0,2	32,6±0,1	31,8±0,2
Platelets, *10^9/l	569,0±0,2	593,3±0,2	544,0±0,2
RDW, %	18,0±0,1	18,0±0,1	17,9±0,1
Lymphocytes, %	74,0±0,2	77,0±0,1	65,0±0,2
Monocytes, %	4,0±0,1	3,8±0,1	4,9±0,1
Eosinophils, %	0,5±0,01	0,3±0,01	0,6±0,01
Bacillary, %	0,5±0,02	0,5±0,01	0,4±0,01
Segmentonuclear, %	21,0±0,1	18,4±0,1	29,1±0,1

Table 9. Effect of the test Astadent gel on peripheral blood composition in female white rats, (M ±m) (after 30 days).

The studied indicators	Control	"Astadent" 43 mg/kg	"Astadent" 86 mg/kg
Leukocytes, *10^9/l	7,7±0,1	7,9±0,1	8,3±0,1
Erythrocytes,*10^{12}/ l	6,0±0,1	6,5±0,1	5,0±0,1
Hemoglobin, g/ l	140,0±0,2	138,0±0,2	136,0±0,1
Hematocrit, %	35,0±0,2	37,0±0,2	32,5±0,2
MCV, Fl.	49,0±0,2	50,4±0,2	58,0±0,2
MCH, picograms	22,0±0,2	26,0±0,2	19,0±0,1
MCHC, g/l	30,0±0,2	41,0±0,3	39,0±0,2
Platelets, *10^9/l	590,0±0,1	615,0±0,2	589,0±0,2
RDW, %	18,0±0,1	23,0±0,1	20,0±0,1

Lymphocytes, %	69,0±0,1	73,0±0,1	65,0±0,2
Monocytes, %	5,0±0,1	3,0±0,1	7,0±0,1
Eosinophils, %	0,9±0,01	0,5±0,01	0,5±0,01
Bacillary, %	0,1±0,01	0,7±0,01	0,6±0,01
Segmentonuclear, %	25,0±0,1	22,8±0,2	26,9±0,1

Tabl. 9

The studies showed that lymphocytes have pycnotized nucleus, granularity is detected. The main mass of segmentonuclear cells has gentle, neutrophilic granularity in smears. Eosinophilic cell nuclei are formed of loose chromatin substance and are almost circular in shape. Monocytes are very different from lymphocytes, equal in size to two erythrocytes, have a large bean-shaped nucleus and a broad protoplasmic border, which is stained blue or purple with delicate granulation. Blood plates lie in large clumps. There were no significant differences between the parameters of the control and experimental groups. No sex differences were found.

Thus, the peripheral blood of rats of all experimental groups after 30 days of application of the test preparation "Astadent" by its quantitative and qualitative composition corresponded to the species physiological norm.

9.7 Influence on biochemical blood parameters.

Table 10 presents the data on the effect of the test drug "Astadent" on the main biochemical indices and on the enzyme activity and blood ion balance of white rats. The study was performed on a biochemical automatic analyzer ILAB 650 (USA).

Table 10. Effect of the test Astadent gel on the main biochemical indices of peripheral blood of white rats, (M ± m).

Indicator	Control	"Astadent" 43 mg/kg	"Astadent" 86 mg/kg
Total bilirubin (BilT), μmol/L	2,2±0,1	2,0±0,2	1,80±0,2
AST, E/l	620,0±0,1	65,3±0,2	64,8±0,2
Creatinine (CREAT)	62,0±0,1	61,8±0,2	63,0±0,2
ALT, E/l	71,2±0,1	71,4±0,1	72,0±0,2
Alkaline phosphatase (ALP), E/l	131,3±0,2	127,5±0,2	135,0±0,2
Glucose (Glu), mmol/l	4,7±0,1	4,5±0,1	4,8±0,1
GGT, E/l	111,5±0,1	112,0±0,1	108,5±0,1
Amylase (AMYL), E/l	641,0±0,1	614,2±0,1	642,0±0,1
Total protein (T PROT), g/l	61,7±0,1	61,9±0,1	64,3±0,1
KFK, E/l	85,0±0,1	86,5±0,1	87,7±0,1
Urea (UREA), mmol/l	5,4±0,1	5,7±0,1	5,9±0,1

As can be seen from the data presented in the table, both the studied gel and the comparison drug in both tested doses have no adverse effect on the main biochemical blood parameters, the activity of blood plasma enzymes and its electrolyte balance.

9.8 Study of possible local irritation

No signs of local inflammatory reaction (infiltration, redness) were registered when applying the studied Astadent gel to the oral mucosa, which was confirmed by visual and histological examination.

The results obtained are presented in Table 11.

Table 11. Registration of local inflammatory response in rats after application of «Astadent» gel

Dose per active ingredient, mg/kg	43	86
1 day		
«Astadent»	0	0
7 day		
«Astadent»	0	0
14 day		
«Astadent»	0	0

10. Conclusion.

In the study of toxicity and possible local irritant effects no complications in the internal organs and local inflammatory response were recorded.

In acute toxicity studies on mice it was shown that the LD50 of the test gel "Astadent" was not established. Subsequent observation of the animals showed no deviations in the appearance, condition of the coat and mucous membranes, character of excretions, behavioral reactions, weight gain.

When applying "Astadent" gel to the mucous membranes of the tested animals, no differences in the manifestation of toxic effects were also noted. Throughout the experiment on evaluation of chronic toxicity in animals treated with "Astadent" gel, no deviations in motor activity were detected. The state of skin, mucous membranes and hair remained normal. The dynamics of changes in the weight of female and male rats during 30 days did not differ from the weight of control animals. The amount of feed and water consumed by the rats receiving the studied preparation did not statistically differ from the parameters of the animals in the control groups.

Orientational motor activity, as an indicator of the central nervous system state, in rats of both sexes that received the test gel with astaxanthin produced by (PFUR, RF) Center for Collective Use (Scientific and Educational Center) of PFUR did not differ from the same indicator in control animals.

The gel had no adverse effects on the peripheral blood parameters and biochemical blood parameters, detoxifying function of the liver.

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

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Lecture

Morphology and physiology of salivary glands.

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Abstract: This article discusses the issues of classification and morphology, ultrastructural features of their cells, embryogenesis. The importance of saliva for the normal functioning of the oral cavity is described.

Keywords: salivary glands, oral fluid, saliva, salivation.

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1. Introduction

The oral cavity is constantly washed with saliva, which performs various functions that ensure the normal functioning of the oral organs: providing local immunity, maintaining the normal condition of the teeth (providing them with calcium and phosphates), moistening the oral cavity, participating in digestive processes, endocrine, excretory, regulation of water-salt homeostasis, etc. [1-3]. Understanding the structure and functions of the salivary glands is relevant for such specialized specialists as dentists [4, 5], otorhinolaryngologists, oncologists [6], maxillofacial surgeons [7], plastic surgeons [8], chemo- and radiotherapists, pathologists [9], etc. [10].

2. Embryogenesis of salivary glands and disorders of their development

The source of the development of salivary glands is the epithelium of the oral cavity. Connective tissue stroma develops from mesenchyma. The submandibular gland is laid at 6-7 weeks of intrauterine development. The parotid gland and sublingual are laid at 8 weeks. At birth, the glands already secrete saliva. Violation of the bookmark and subsequent development of the salivary glands leads to malformation – aplasia. With heterotopia, the gland lining shifts compared to the norm, while the topography of the gland is disturbed, which can complicate surgical interventions [11].

Among the possible pathologies in the duct system, agenesis and aplasia occur. Hypoplasia and atresia of the main ducts are very rare. On the contrary, intra-nodal (intranodal) heterotopias are quite common [12], tumors of the salivary glands occupy 3-5% of all tumors of the head and neck [13]. Extranodal heterotopia is rare, but it can involve the pituitary gland and the lower jaw, the lower part of the neck, and the thyroid gland. In 20% of people there are additional parotid glands, separated from the main gland, but adjacent to the excretory duct of the parotid gland (Stensen's duct).

3. Classification and general principles of the structure of the salivary glands

The salivary glands are divided into the glands of the vestibule of the mouth and the glands of the oral cavity proper. The glands of the oral cavity include 3 pairs of large salivary glands (parotid, submandibular and sublingual) [5]. Salivary glands located in the mucous membrane of various parts of the oral cavity (buccal, labial, tongue glands, palatine tonsils, larynx, pharynx) are called small salivary glands [14].

3.1 The large salivary glands

The large salivary glands are complex, branched alveolar (parotid) or alveolar-tubular (submandibular, sublingual) glands, have one principle of anatomical organization – a branched system of excretory ducts and secretory terminal sections (Fig. 1).

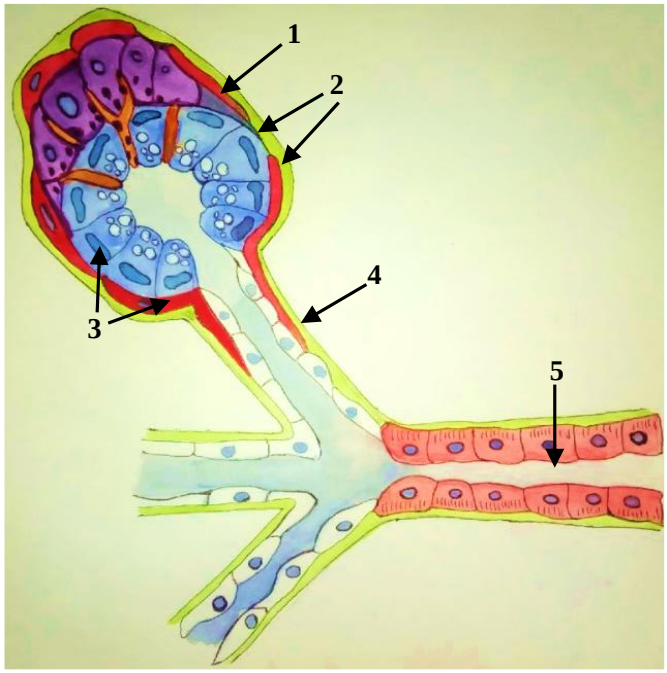

Figure 1. Diagram of the structure of the secretory department and ducts of the salivary gland. 1 – serous cells; 2 – mucous cells; 3 – myoepithelial cells; 4 – insertion duct; 5 – striated duct.

Inside the lobules, there are intra-lobular excretory ducts and numerous secretory terminal sections. All connective tissue structures form the stroma, and epithelial cells (ducts and secretory departments) form the parenchyma of the gland [15]. The secretory divisions of the salivary glands consist of secretory and myoepithelial cells, are divided into protein (serous), mucosal (mucosal) and mixed (protein-mucosal). The protein end sections have a rounded shape in the form of alveoli with a narrow lumen. They consist of serous cells shaped like a truncated pyramid. The cell nucleus is rounded, the cytoplasm contains a well—developed granular endoplasmic network that provides basophilia when sections are stained with hematoxylin and eosin (Fig.2), the Golgi complex, numerous mitochondria in the basal part of the cell and an abundance of apically located secretory granules rich in protein - ptyalin (amylase), lysozyme, lactoferrin [15].

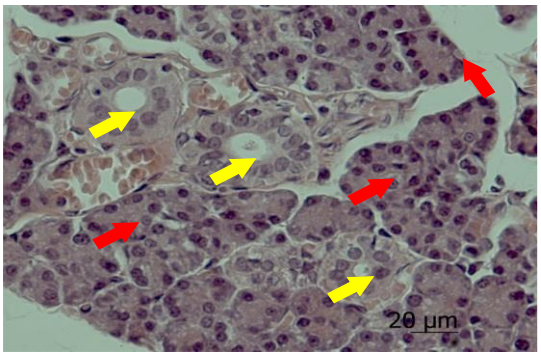

Figure 2. Protein secretory departments. Red arrows – secretory departments, yellow arrows – excretory ducts. Parotid salivary gland. Stained with hematoxylin and eosin. Magnification x 300.

The mucous end sections predominate in the sublingual salivary gland (Fig. 9). They are larger and lighter than the protein ones, have a tubular shape. Mucous cells resemble protein cells in shape, but their nuclei are located basally and are not round, but flattened, there are fewer mitochondria in the cytoplasm, a less developed granular endoplasmic network, but a significantly more significant Golgi apparatus, which indicates a greater proportion of the carbohydrate component in their secret. Most of the cytoplasm is filled with a mucous secretory product having a light cellular appearance [11, 16-18].

The mixed terminal sections consist of 2 types of glandular cells – protein and mucous, especially clearly visible in the submandibular salivary gland (Fig. 4, 8). Protein and mucous cells are located in the mixed secretory department alternately, directing the mixed secret into the duct.

Many authors point to serous half-moons, or Gianuzzi half-moons (Fig. 4), which are only a consequence of the preparation of the drug, that is, an artifact [11].

Each terminal section is surrounded by myoepithelial cells, which have a process shape, in their cytoplasm there are numerous contractile actin and myosin filaments, as well as intermediate filaments that belong to the cytokeratin family, which makes it possible to indicate the source of their development ectoderm, not mesenchyma. The contraction of these cells promotes the excretion of saliva from the terminal sections [19].

The excretory ducts transport and modify saliva before it enters the oral cavity. In the large salivary glands, insertion, striated, interlobular and common excretory ducts are represented [15]. The insertion ducts form the beginning of the duct system, they are thin tubes lined with a single layer of cubic cells (Fig.3). On sections stained with hematoxylin and eosin, they differ in basophilic coloration and small diameter (less than the diameter of the secretory department). The insertion ducts are very well developed and branched in the parotid salivary gland [11].

The insertion ducts merge with each other, forming striated excretory ducts (Fig. 3), lined with a single layer of prismatic or cubic cells, the basolateral membranes of which have a pronounced folding (striation) due to mitochondria located between numerous folds of the plasmolemma.

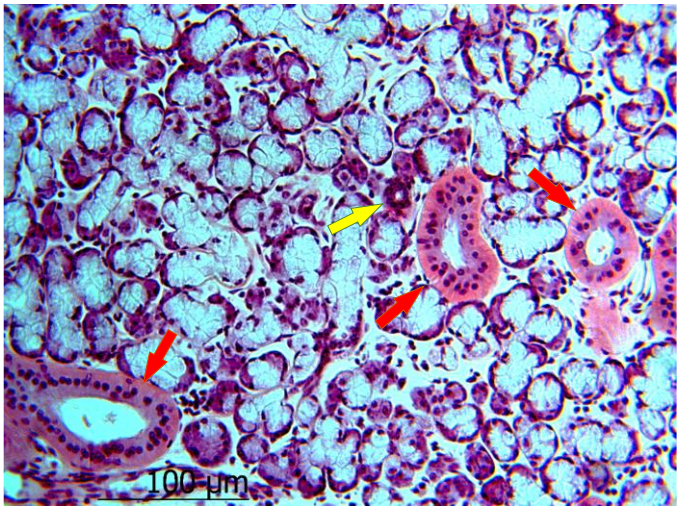

Figure 3. Striated ducts (red arrows) and insertion duct (yellow arrow). Stained with hematoxylin and eosin. Magnification x 200.

The striated excretory ducts connect to each other, forming intra-lobular ducts (Fig. 4) of a larger diameter, lined with a double-row or double-layer epithelium. The excretory ducts extending from the lobules combine to form interlobular excretory ducts, which are lined with a multilayer cubic epithelium Fig. 5).

The common (main) excretory duct of the gland approaches the mucous membrane of the oral cavity, opens on its surface, its mouth is lined with a multilayer flat epithelium.

The interlobular connective tissue forming the stroma of the glands contains fat cells, vessels, nerves and interlobular excretory ducts [20, 21]. The small salivary glands are located in almost all parts of the oral mucosa, except for the gums and the anterior part of the hard palate. They are predominantly mucous by the nature of the secretion, their ducts are not differentiated into inset and striated. Despite its small size, the importance of small salivary glands is due to their ubiquity in the oral mucosa and their abundance [22].

3.2 The small salivary glands

The small salivary glands also play an important role in the formation of protective functions and moistening of the mucous membrane due to the composition of the saliva secreted by them [23, 24]. They produce about 70% of saliva mucins and a significant amount of immunoglobulins (mainly secretory IgA), salivary acid phosphatase and lysozyme, preventing the colonization of microorganisms on the surface of teeth and the occurrence of infections. The structure and function of the large and small salivary glands are potentially affected by alcohol and drug use, as well as poor nutrition, aging and radiation therapy of the head and neck [25, 26].

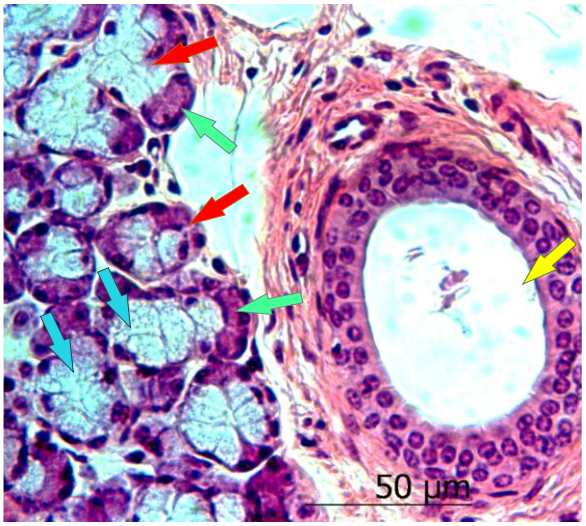

Figure 4. Interlobular excretory duct (yellow arrow); mixed secretory sections (red arrows), which consist of mucosal (mucous) cells (blue arrows) and serous cells forming serous Gianuzzi half-moons (green arrows). Stained with hematoxylin and eosin. Magnification x 300.

4. Saliva and oral fluid

The salivary glands produce saliva, which when it enters the oral cavity is called oral fluid [27]. It contains the secret of the large and small salivary glands, the contents of the dental grooves, bacteria, food particles, leukocytes, etc. Oral fluid has bacteriostatic properties, protects teeth by participating in the remineralization of enamel, forms a protective film of calcium-binding proteins, facilitates articulation of speech and the act of swallowing, moistening a lump of food. Due to a pH of 5.9-7.6, saliva has buffering properties that ensure the neutralization of acids. The components of the oral fluid are involved in the process of blood clotting and wound healing due to the presence of clotting factors and epidermis growth factor in it [28].

4.1 Salivation

Salivation of large salivary glands is carried out reflexively. Small salivary glands secrete constantly, moistening the mucous membrane of the oral cavity. Regulation of salivation is carried out by nerve centers located in the medulla oblongata, hypothalamus and cerebral cortex. The formation of a conditioned reflex mechanism occurs when visual, auditory, and olfactory receptors are irritated. In humans, conditioned reflex secretion of saliva can also begin with the memory of delicious food. When parasympathetic nerve fibers are stimulated, a large volume of watery saliva with a low protein content and high concentrations of electrolytes is secreted [29]. When sympathetic nerve fibers are stimulated, a small volume of viscous saliva with a high content of mucus is released [30].

The secretion of saliva in the glands takes place in two stages. At the initial stage, acinar cells form a primary isotonic secret – primary saliva. Then, the primary secretion is modified in the ducts of the glands, depending on its composition and physiological needs – secondary saliva. By the striated cells of the excretory ducts, excess hydrogen, chlorine and sodium ions from the gland duct are reabsorbed back into the blood using passive transport, which leads to a decrease in the acidic reaction of saliva. And potassium ions and HCO_3^- from blood serum and tissue fluid selectively enter saliva by active transport, increasing its alkaline reaction. Due to this mechanism of regulation, the pH of the saliva secreted may differ significantly from the always stable blood pH value of 7.4 [31].

Normally, a person releases up to 2 liters of saliva per day. Due to the strengthening of both salivary reflexes and spontaneous salivation, the amount of saliva can increase several times (hypersalivation). Hypersalivation is observed in people suffering from Parkinson's disease, epidemic encephalitis, cerebrovascular accident, stomatitis, toxicosis of pregnant women, helminthiasis, trigeminal neuralgia. At the same time, increased salivation (ptialism) may be such that the patient is unable to swallow saliva. A decrease in saliva secretion (i.e. hyposalivation) is accompanied by dryness of the oral mucosa — xerostomia, often complicated by caries, stomatitis, fungal infections. Hyposalivation (hyposialy, sialopenia) and asialia (i.e. extreme hyposalivation) are symptoms of both common diseases (septic conditions, pneumonia, diabetes, malignant anemia, typhoid and typhoid fever, etc.) and pathology of the salivary glands proper, their inflammation (sialodenitis), blockage of the excretory ducts (sialolithiasis). With age, the salivary glands may

be subject to atrophic changes, which often leads to hyposalivation, and as a consequence, to xerostomia. [32].

During the SARS-COV-19 pandemic, salivary glands were found to be susceptible to coronavirus infection. Thus, several studies have shown that saliva and destroyed epithelial cells of the salivary glands may contain SARS-COV-2 [21, 33]. This is of great diagnostic importance, since the detection of coronovirus in the material obtained from the mucous membranes is possible only at the initial stages of the lesion, when there are no clinical symptoms, and the isolation of viruses into saliva can help with the verification of the virus strain at an early stage of clinical manifestations [5].

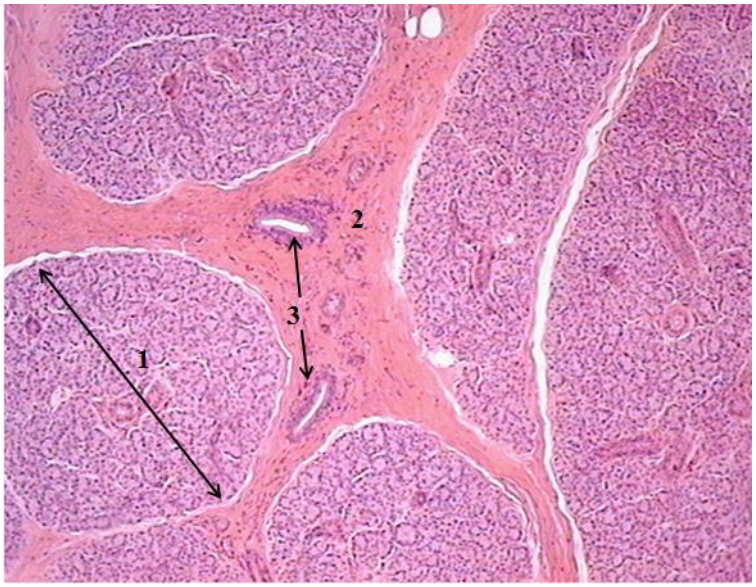

Figure 5. Parotid salivary gland, lobules (1), interlobular connective tissue (2), interlobular excretory ducts (3). Stained with hematoxylin and eosin. Magnification x 150.

4.2 The parotid gland

The parotid gland is the largest salivary gland, has a mass of 20-30 g, produces 30% of the total amount of saliva. The connective tissue capsule of the gland is well developed, numerous partitions depart from it, which divide the gland into lobes and lobules (Fig. 5). The parotid salivary gland produces a protein secret, therefore, basophilia is characteristic of secretory cells when stained with hematoxylin and eosin [25].

On electron microphotographs, numerous secretory granules are visible in the apical areas of serous cells, (Fig. 6, 7) filled with an electron-dense product. In saliva produced by the parotid gland, there is a high level of the enzyme saliva amylase (ptyalin) and secretory IgA. The main excretory duct (Stensen's duct, Stenon's duct) of the parotid salivary gland opens into the oral cavity near the second molar of the upper jaw.

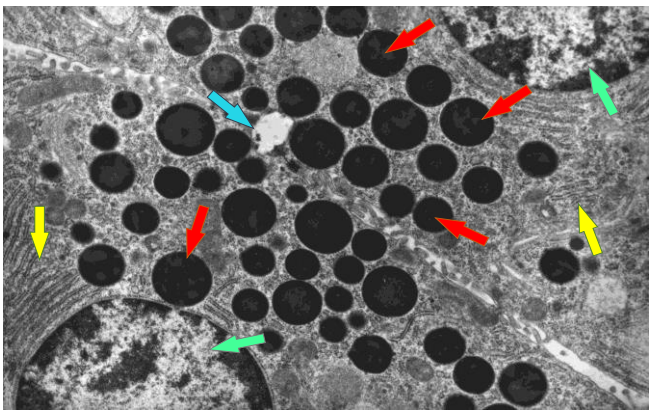

Figure 6. Ultrastructure of parotid salivary gland cells before meals: secretory granules (red arrows), granular endoplasmic network (yellow arrows), cell nuclei (green arrows) and the lumen of the secretory department (blue arrow). Magnification x 5300.

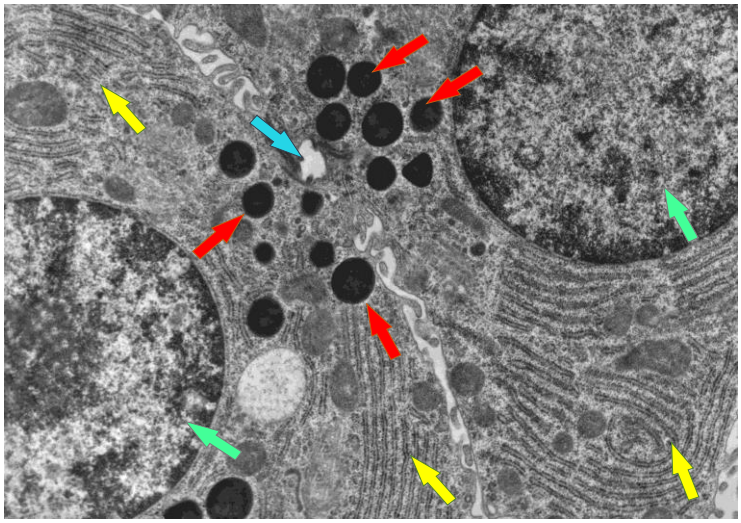

Figure 7. Ultrastructure of parotid salivary gland cells in the conditioned reflex phase of saliva secretion during meals: secretory granules (red arrows), granular endoplasmic network (yellow arrows), nuclei of neighboring cells (green arrows) and acinus lumen. (blue arrow) Magnification x5300.

4.3 The submandibular gland

The submandibular gland is much smaller than the parotid gland, has a mass of 12-15 g, but produces approximately 60% of the total volume of saliva. This gland is mixed with a predominance of the serous component (Fig. 8). The striated excretory ducts of the submandibular gland are significantly longer than the ducts of the parotid or sublingual glands; as a result, numerous cross-cut profiles of these excretory ducts are visible on histological sections, which is a characteristic feature of the submandibular gland. The main excretory duct is called Wharton's duct (Wharton's duct), it opens into the oral cavity under the tongue at the frenulum with a thickening – a sublingual caruncle [32].

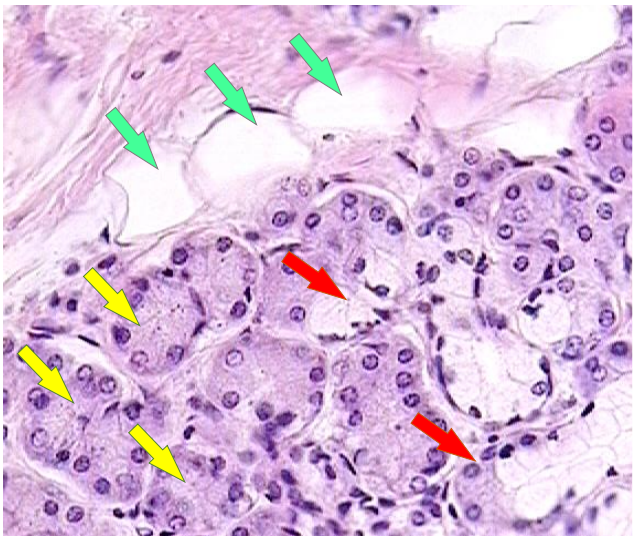

Figure 8. Submandibular salivary gland: mixed terminal divisions (red arrows), serous terminal divisions (yellow arrows) and fat cells (green arrows). Stained with hematoxylin and eosin. Magnification x 375.

4.4 The sublingual gland

The sublingual gland, the smallest in the considered group of salivary glands, almond-shaped, produces only about 5% of the total volume of saliva, in which the mucous component predominates. On a preparation stained with hematoxylin and eosin, the sublingual gland looks very light due to the abundance of mucous secretory departments (Fig. 9). The sublingual gland has a loose connective tissue capsule, and its system of excretory ducts does not form a common excretory duct. Several excretory ducts open in the area of the bottom of the oral cavity and along the course of the excretory duct of the submandibular gland [35].

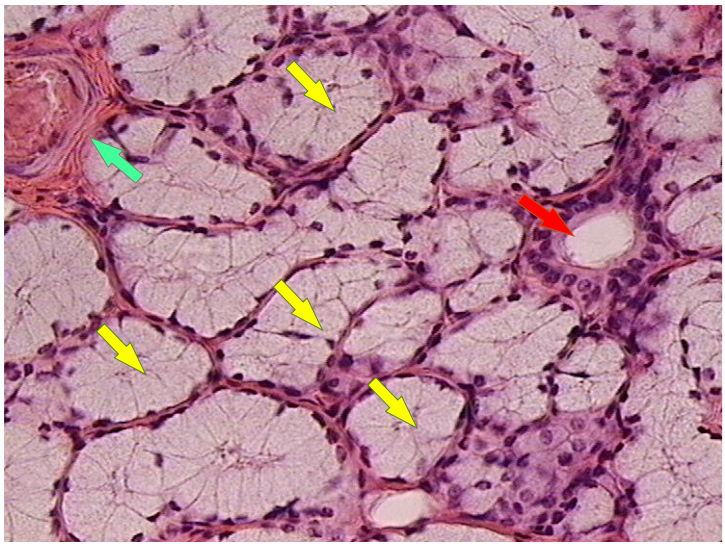

Figure 9. Sublingual salivary gland: mucous end sections (yellow arrows), intra-lobular excretory duct (red arrow) and artery (green arrow). Stained with hematoxylin and eosin. Magnification x 375.

Relatively recently, the tubal, or Eustachian glands, located in the submucosal base of the auditory tube, which a number of scientists refer to the salivary glands, have been described. These glands contain mixed (serous-mucous) secretory departments that play a physiological role in the lubrication of the nasopharynx and when swallowing. However, localization of these glands and saliva secretion is not carried out in the oral cavity, which means that it is impractical to refer them to salivary glands. [36, 37,38].

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