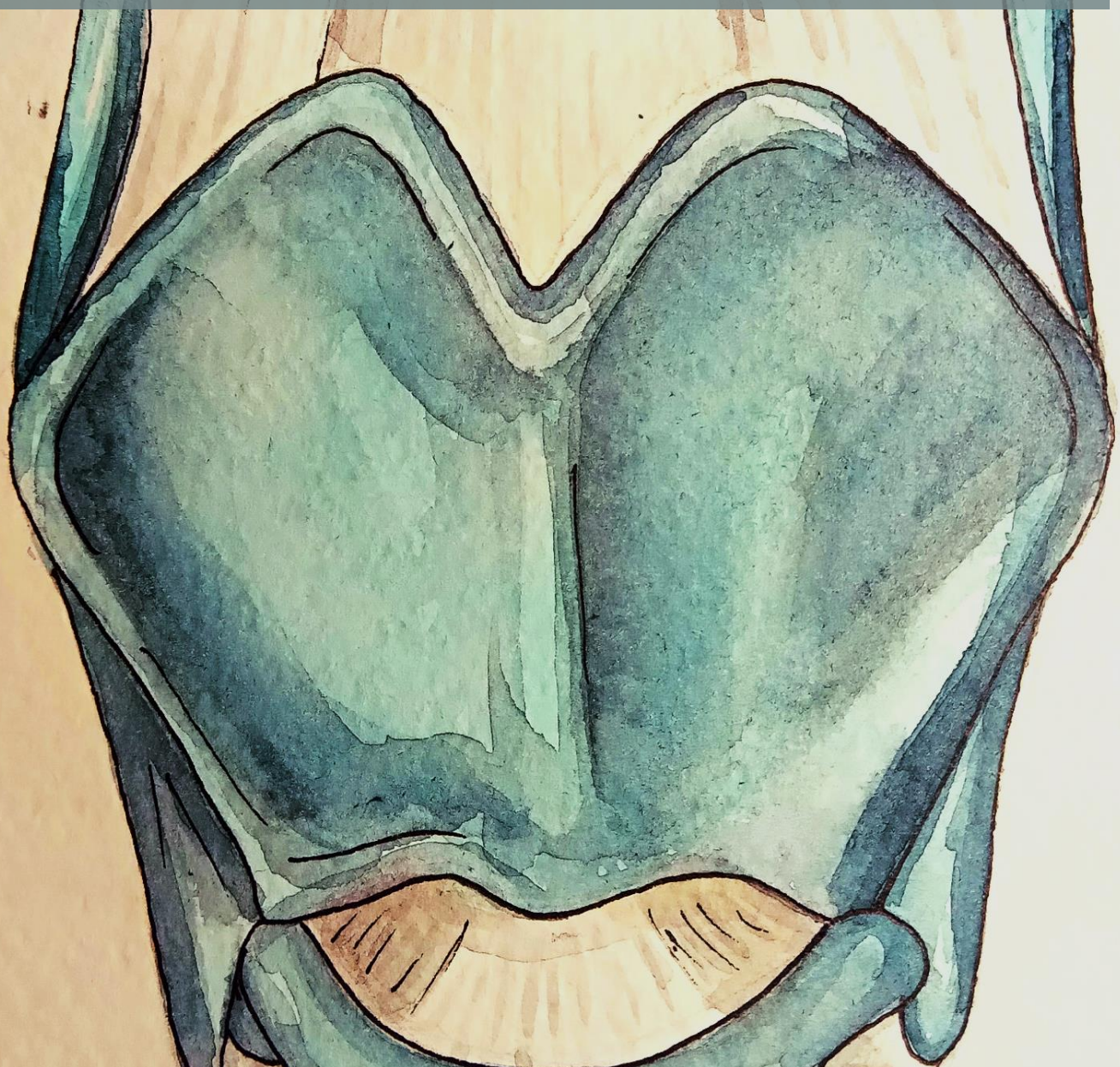
OTORHINOLARYNGOLOGY, HEAD and NECK PATHOLOGY (ORLHNP)

2024 | Vol 3 | N 2 ISSN 2989-1523

Journal of International Society for Clinical Physiology & Pathology



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OTORHINOLARYNGOLOGY, HEAD and NECK PATHOLOGY (ORLHNP)

2024 | Vol 3 | N 2 ISSN 2989-1523 (Online)

Journal of International Society for Clinical Physiology & Pathology

Interdisciplinary medical reviewed journal
The authors declare that they have no competing interests
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ISSN 2989-1523 = Otorhinolaryngology, Head and Neck Pathology (Online)
COBISS.CG-ID 25846788

Website of ISCPP: https://iscpp.eu/
Website of ORLHNP: https://orlhnp.iscpp.eu/

Editor office address: 85347 Norveska, 5, Igalo, Herceg Novi, Montenegro
E-mail: orlhnp@iscpp.eu

Contents

Review

The Feasibility of Implanting Multifocal Intraocular Lenses in Patients with Glaucoma.

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Abstract: The article provides a literary review of the latest data and recent studies on the effect of multifocal intraocular lens implantation on ocular functions and quality of life in patients with glaucoma. One of the most common problems of modern ophthalmological practice is the presence of combined ocular pathology in patients. The presence of cataracts and glaucoma in a patient increases the risk of developing blindness. The presence of cataracts can contribute to the progression of glaucoma due to the increased size of the lens, which, acting on the iris, displaces it, thereby making the angle of the anterior chamber already from the initial anatomical parameters of a particular eye. This change leads to an increase in intraocular pressure and the progression of glaucoma. Cataract surgery with IOL implantation provides a good opportunity to improve the quality of vision in patients with POAG. To date, there are several types of IOLs on the market, the implantation of which is considered individually for each patient to achieve maximum results. One is the most popular IOL that patients choose is multifocal IOL. Multifocal IOLs provide optimal vision in the distance, at medium and close distances, after implantation of this type of IOL, eyeglass correction is not required. However, multifocal IOLs have several disadvantages: have an increased light scattering effect, it is not uncommon after implantation to experience a decrease in the quality of vision, which leads to problems, especially in dim lighting, patients often complain about the presence of photopsia. Due to the prevalence of combined cataracts and glaucoma, as well as the increased popularity of multifocal IOLs, the question arises whether it is advisable to implant these types of intraocular lenses in patients with glaucoma. The urgerncy of the problem is the small number of studies in this area.

Keywords: keywords.

Citation: Petrov A. The feasibility of implanting multifocal intraocular lenses in patients with glaucoma. Otorhinolaryngology, Head and Neck Pathology (ORLHNP). 2024; 3 (2): 4-8.

https://doi.org/10.59315/ORLHNP.2024-3-2.4-8

Academic Editor: Valentin Popadyuk

Received: 15.06.2024
Revised: 22.06.2024
Accepted:30.06.2024
Published: 1.07.2024

Publisher's Note: International Society for Clinical Physiology and Pathology (ISCPP) stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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Introduction

One of the most common problems of modern ophthalmological practice is the presence of combined ocular pathology in patients. For example, the risk of combined glaucoma and cataract in patients increases with age. The presence of cataracts and glaucoma in a patient increases the risk of developing blindness. According to various data, the prevalence of this combined pathology varies from 17.0 to 38.6%. [1,2].

According to multiple estimates, approximately 57.5 million people worldwide suffer from primary open-angle glaucoma (POAG), and the total prevalence of the disease is 2.2%. In Europe, approximately 7.8 million people suffer from POAG, with a prevalence of 2.51%. It is expected that by 2040, approximately 111.8 million people worldwide will be diagnosed with primary open-angle glaucoma [2].

In the Russian Federation, the total prevalence of POAG in 2019 was 1.3 million people. An increase in the prevalence and incidence of POAG in the Russian Federation is expected in the next 15 years [3].

It is worth because eye structures such as the drainage system, ciliary body, lens, zonular ligaments are involved in the formation of the anterior and posterior chambers of the eye. Based on this, these structures form a morphofunctional integrated system, the destabilization of which can lead to such changes as impaired hydrodynamics, microhemodynamics, and dystrophic changes of the most discussed conditions is the effect of an enlarged lens size. The presence of cataracts can contribute to the progression of glaucoma due to the increased size of the lens, which, acting on the iris, displaces it, thereby making the angle of the anterior chamber already from the initial anatomical parameters of a particular eye. This change leads to an increase in intraocular pressure and the progression of glaucoma. Currently, there is evidence that cataract surgery can lead to a decrease in intraocular pressure (IOP) [4].

It is also worth emphasizing the indirect effect of glaucoma on the development of cataracts. Glaucoma itself does not cause cataracts, although there are certain situations where cataracts progress as a result of surgical treatment of glaucoma. For example, glaucoma surgeries such as trabeculectomy or implantation of drainage devices are known to accelerate the process of cataract formation to some extent [4].

Cataract surgery provides a good opportunity to improve the quality of vision in patients with POAG. Great achievements in the development of modern intraocular lenses (IOL) and improvements in the technique of cataract surgery can ensure independence from wearing glasses in individual patients and maximize the quality of vision.

Cataract surgery is the most frequently performed ophthalmic surgery, in 2020 the number of people requiring cataract surgery worldwide increased to 30.1 million, which is 50% more than in 2000. According to 2020 data, 460-480 thousand cataract surgeries are performed annually in Russia [5, 6].

In the presence of combined cataracts and glaucoma, there is a dilemma of what should be operated on first and how to resolve this situation. There are three surgical approaches to solving this problem:

1) cataract extraction with IOL implantation.

2) two-stage surgical treatment.

3) combined simultaneous intervention with IOL implantation [7].

The choice of tactics for the treatment of combined pathology depends on a number of factors, such as: the stage of glaucoma, stabilization of the glaucoma process, the level of intraocular pressure, hypotensive regime, the degree of maturity of the cataract, the size of the lens.

As noted above, cataract surgery is the most sought-after surgical treatment in ophthalmic practice. In case of combined cataract and glaucoma, cataract extraction alone is recommended, according to a few authors, in the presence of initial, immature or mature cataracts, compensated IOP levels when using a minimal hypotensive regimen by the patient, as well as stabilization of the glaucoma process according to perimetry data [8,9].

Two-stage treatment of a patient with a combined pathology is recommended in cases where the degree of maturity of the cataract corresponds to an initial or immature one with concomitant unstable glaucoma and uncompensated IOP at maximum hypotensive mode. At the same time, it is advisable to perform anti–glaucoma intervention at the first stage, and then, no earlier than 6 months later (after the formation of outflow pathways), approach the second stage of treatment - cataract extraction [10, 11].

In recent years, performing combined surgery for combined cataract and glaucoma has been gaining popularity. This method of surgical treatment solves two problems simultaneously: in the postoperative period, visual acuity increases, and IOP levels are compensated [12].

It has been proven that the degree of IOP reduction in patients after combined surgery is greater than in patients after cataract extraction [13].

Types of IOL

To date, there are several types of IOLs on the market, the implantation of which is considered individually for each patient to achieve maximum results:

- Monofocal IOLs provide optimal visual acuity (far or near) at a certain distance, depending on the calculation. After implantation of this type of IOL, the patient requires a point correction depending on the initial calculation parameters [14].
- Toric monofocal IOLs provide optimal visual acuity in patients with astigmatism without subsequent cylindrical eyeglass correction. However, after implantation of this type of IOL, the patient will need spherical correction for short or long distances, depending on the parameters of the initial calculation [12].
- Multifocal IOLs provide optimal vision in the distance, at medium and close distances, after implantation of this type of IOL, eyeglass correction is not required. However, multifocal IOLs have several disadvantages:

- have an increased light scattering effect. This feature leads to a decrease in contrast.
sensitivity.
- it is not uncommon after implantation to experience a decrease in the quality of vision, which leads to problems, especially in dim lighting,
- patients often complain about the presence of photopsia [5].

- Multifocal Toric IOLs make it possible not only to correct astigmatism, but also to provide acceptable visual acuity at different distances [12].
- IOL with increased depth of focus is a completely new category of intraocular lenses for correction of presbyopia, designed to expand the range of vision, smooth transition of focal length from medium to near distance, while, unlike multifocal lenses, photopsia occur less frequently [15].

● Accommodative IOLs This type of IOL can provide optimal visual acuity at various distances using similar accommodative mechanisms as the native lens. The work of this type of IOL is based on a change in its anterior -posterior position under the action of the ciliary muscle [16].

Contrast sensitivity

As noted above, the main advantage of multifocal IOLs is that this type of intraocular lens is able to provide vision at several distances without resorting to eyeglass correction. However, as has already been proven based on numerous studies, multifocal IOLs reduce contrast sensitivity. As it was found, after passing through a multifocal IOL, less than 50% of the light rays are directed to one of several main focus.

Therefore, it is logical to assume that image focusing occurs with a certain loss of contrast sensitivity. The human visual system (photoreceptors, visual pathway, and tract, as well as the occipital cortex of the brain) is able to minimize the manifestations of blurred images and improve image focusing [17].

Vingolo E.M. et al. In 2007, the visual acuity and contrast sensitivity of patients without concomitant ocular pathology who were implanted with a multifocal IOL were compared with patients without concomitant ocular pathology who were implanted with a monofocal IOL. According to the results of the study, multifocal IOL provided lower contrast sensitivity than monofocal IOL [4, 18].

In 2013, Nancy Aychoua et al. published the results of a study where compared the quality of contrast sensitivity in patients with phakic and artificial eyes. In the study, the patients were divided into 3 groups. The first group included 16 patients with implanted multifocal IOLs, the second group consisted of 18 patients with a native lens as a control group, the third group included 12 patients with implanted monofocal IOLs. The average age of the patients in the three groups was 64 years without concomitant ocular pathology. Contrast sensitivity was assessed using the Humphrey Field Analyzer perimeter (Carl Zeiss Meditec Inc.) in the 30-2 program. The results of the study showed that MD, on average, was 2.40 dB lower in the group of patients with multifocal IOLs compared with the control group and 0.32 dB lower compared with the group of patients with monofocal IOLs (p=0.52) [19].

Historically, for patients who are recommended cataract surgery and who have POAG as a concomitant ocular pathology, a systematic approach to the choice of IOL is necessary.

Due to the prevalence of combined cataracts and glaucoma, as well as the increased popularity of multifocal IOLs, the question arises whether it is advisable to implant these types of intraocular lenses in patients with glaucoma. The urgency of the problem is the small number of studies in this area.

Glaucoma and contrast sensitivity

It is known that in glaucoma, the patient suffers from contrast sensitivity, the severity of which directly correlates with the degree of structural and functional damage to the nerve fibers of the ZN and SNVS.

Iancu R. Et al. come to conclusion that patients in the early stages of glaucoma often notice a decrease in vision than could be expected. This feature is most likely associated with the presence of concomitant ophthalmological pathology, as well as a decrease in photosensitivity due to the presence of glaucoma. In addition, patients with glaucoma notice a decrease in the ability to see optimally in low-light conditions, as well as the ability to detect low-contrast objects [20].

Clinical features after multifocal IOL implantation in healthy patients and patients with glaucoma

Healthy people may not even notice a decrease in contrast sensitivity after implantation of multifocal IOLs. However, the combination of IOLs (in particular multifocal IOL) in the eye with an already progressive loss of contrast sensitivity due to glaucoma causes much more concern [21].

The difficulties in choosing multifocal IOL in patients with glaucoma are based on a decrease in contrast sensitivity after implantation of this type of IOL, especially in the advanced and advanced stages of glaucoma, as well as these fields of vision. However, there is evidence from scientific research that in the initial stage of glaucoma with compensated IOP and the patient's desire, multifocal IOL implantation can be carried out. Optimization of the control of such patients should be carried out with careful monitoring of the IOP level, the state of the IOP and the visual fields, since the progression of glaucoma optic neuropathy in patients with implanted multifocal IOLs can lead to an even greater loss of contrast sensitivity [22, 23].

A large percentage of patients with combined glaucoma and cataract expect high visual acuity and refusal to wear glasses after cataract surgery. Thus, the main question arises – Is it advisable to implant multifocal IOLs in these patients [22]

It is worth noting that some patients with glaucoma often have a narrow pupil size. This feature should be considered when choosing multifocal IOLs. The fact is that in the refractive-diffractive design of this type of intraocular lens, the distribution of light varies depending on the size of the pupil, so in large pupils most of the light is directed at a distance, and in small ones the light splits. This phenomenon can lead to additional photopsia and defocusing at different distances in patients with glaucoma [24, 25].

According to literature sources, pseudoexfoliation syndrome is the basis for the occurrence of POAG in some patients. The presence of this syndrome is associated with an increased risk of instability of the zinc ligaments. Considering that multifocal IOLs require perfect alignment, as well as stability of the capsule bag and zinc ligaments. Thus, it is advisable to avoid implantation of myoles in this group of patients. The weakness of the zonular apparatus can lead to the descentration of multifocal IOLs, thereby not satisfying the final and expected results from implantation of this type of IOL [24,25].

Currently, there is insufficient scientific data from large-scale studies on the feasibility of implantation of multifocal IOLs in patients with glaucoma, which makes this research vector relevant.

The study conducted by Carmen Sánchez-Sánchez et al involved 38 patients aged 57 to 88 years, who were divided into 4 groups: the first group included 11 patients without concomitant ocular pathology (control group), the second included 9 patients with preperimetric glaucoma, the third group included 9 patients with advanced and far-advanced stage of glaucoma, 9 patients with a dry form of AMD were included in the fourth group. The authors concluded that the implantation of multifocal IOLs in patients with glaucoma (in particular, in patients with advanced and advanced stage of glaucoma) is impractical, because these patients had lower spatial contrast sensitivity than in the group of patients without concomitant ocular pathology, the group of patients with preperimetric glaucoma and the group of patients with dry form AMD. In addition, it was shown that the group of patients with implanted multifocal IOL and glaucoma experienced more difficulties when driving at night and complained of more frequent glare than patients from the group of patients without concomitant ocular pathology and the group of patients with preperimetric glaucoma. Patients with glaucoma and dry AMD after implantation of a multifocal IOL required eyeglass correction for nearness more often than in the other two groups [5].

Kameth GG et al. In 2000, a large-scale study was conducted, which included 133 patients with cataracts and concomitant ocular pathology, including 33 patients with various stages of glaucoma. The average age of the patients was 73.2±3.2. Multifocal IOL was implanted in 11 patients with glaucoma, in turn, monofocal IOL was implanted in 12 patients with glaucoma. The authors concluded that the only difference in the results of patients with monofocal and multifocal IOLs was an improvement in visual acuity without near correction in patients with multifocal IOL implants [26].

Conclusion

The implantation of multifocal IOLs in patients with cataracts and concomitant glaucoma is controversial. The rate of progression optic nerve damage because of glaucoma, the anatomical feature of the eye in these patients, and the ability to reduce the contrast sensitivity of multifocal IOLs make it difficult to decide on the implantation of this type of intraocular lenses.

The lack of large, randomized trials of the use of multifocal IOLs in patients with glaucoma makes it difficult to generalize clear indications for the use of these types of IOLs.

To date, the main decision-making for the implantation of multifocal IOLs is based on an individual approach, the postoperative result of which may not meet the expectations of both the surgeon and the patient himself.

Based on all the above, the goal of subsequent research in this area is a clear determination in determining the indications and contraindications for the implantation of multifocal IOLs.

The goal is to meet the patient's expectations without adversely affecting the progression of glaucoma.

Application of artificial intelligence:

The article is written without the use of artificial intelligence technologies.

Author Contributions: Conceptualization, I.K., V.P. and I.R.; methodology, G.M. and Iv.K.; software, G.M.; validation, M.K., E.S., I.K. and G.M.; formal analysis, V.A.; investigation, I.K. and G.M.; resources, X.X.; data curation, K.L..; writing—original draft preparation, K.I. and G.M.; writing—review and editing, V.P., I.R. and E.S..; visualization, V.P.; supervision, K.L.; project administration, I.K. All authors have read and agreed to the published version of the manuscript."

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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Clinical case

Rare cause of respiratory distress syndrome in a child: Hamartoma of salivary gland in the nasopharynx.

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Citation: Alekseenko S., Tikhomirova E., Serikova E., Barashkova V., Prodanovich E., Turieva V. Rare cause of respiratory distress syndrome in a child: Hamartoma of salivary gland in the nasopharynx. Otorhinolaryngology, Head and Neck Pathology (ORLHNP). 2024; 3 (2): 9-14.

https://doi.org/10.59315/ORLHNP.2024-3-2.9-14

Academic Editor: Valentin Popadyuk

Received: 15.06.2024
Revised: 22.06.2024
Accepted:30.06.2024
Published: 2.07.2024

Publisher's Note: International Society for Clinical Physiology and Pathology (ISCPP) stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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Abstract: *Relevance.* Hamartoma of salivary gland or salivary gland anlage tumor (SGAT) is an extremely rare pathology found mainly in children in the early months of life. *Description of the clinical observation.* This article presents a clinical case of respiratory distress syndrome in a 4-month-old child arisen due to a salivary gland hamartoma in the nasopharynx. The symptoms are nonspecific and are mainly represented by respiratory distress syndrome, difficulty in feeding, apnea, and sleep breathing disorders. SGAT is most commonly found in children in the first months of life, but there are cases of later onset. SGAT is a benign neoplasm, and surgical resection is the main treatment option. SGAT is characterized by the absence of recurrence after removal. The histological picture is a combination of epithelial and mesenchymal components. *Conclusion.* SGAT – a rare benign nasopharyngeal neoplasm in a child in the first months of life. Early diagnostics including endoscopic examination of the nasopharynx, CT and MRI examinations allowed us to determine the operative treatment tactics, achieve a good functional result in the form of complete relief of the child's complaints and prevent development of serious complications related to the upper airway obstruction.

Keywords: hamartoma of the salivary gland, respiratory distress syndrome, salivary gland anlage tumor, nasopharyngeal neoplasm in a child, congenital pleomorphic nasopharyngeal adenoma, benign nasopharyngeal neoplasm.

Introduction

Upper airway obstruction in infants is a frequent and potentially dangerous condition requiring hospitalization and careful examination. In most cases, these symptoms are non-specific and are present in the form of respiratory distress syndrome. The leading causes of persistent nasal airway obstruction in infants are choanal atresia and congenital deformities of the facial skull. Congenital neoplasms of the nasal cavity and nasopharynx are not frequent, but can also lead to marked nasal breathing disorders. A very rare congenital nasopharyngeal neoplasm presented in our clinical case is a hamartoma of salivary gland conception, or congenital pleomorphic adenoma found in a 4-month-old child.

Clinical case

In January 2023, patient N., 4 months 1 week old male, was admitted to the Children's Clinical Center of High Medical Technologies of St. Petersburg named after K.A. Raukhfus with complaints of shortness of breath, cough, and distant wheezing. It is known that he had previously been treated at the Research Institute of Pediatric Infections for acute bronchiolitis, but due to persisting symptoms of bronchoobstruction against the background of decreasing doses of inhalation drugs (Berodual, Budesonide) he was transferred to the specialized pulmonology department of the Raukhfus Children's Clinical Center of High Medical Technologies. According to his mother, in the first month of life the child had poor weight gain, noisy breathing through the nose. Due to her complaints, at the age of 3 months the child

underwent nasopharyngeal cavity and nasopharynx fibroscopy, but the report of nasopharyngeal neoplasm was not described, and the diagnosis was "deviation of nasal septum".

At the Children's Clinical Center of High Medical Technologies of St. Petersburg named after K.A. Raukhfus, a video tracheobronchoscopy was performed through a laryngeal mask, the conclusion being: bilateral catarrhal endobronchitis II stage with diffuse putreform hypersecretion and signs of impaired drainage function. CT scan of the thoracic cavity showed a picture of bronchiolitis.

Despite the treatment of the underlying disease received by the child, the complaints of nasal breathing difficulties persisted. In order to verify the cause of nasal obstruction, the child underwent a number of additional examinations. Under general anesthesia, the nasal cavity and nasopharynx were examined with a 2.7 mm fibroscope, as a result a volumetric smooth formation on a stem was found in the nasopharynx (Fig. 1 a, b), almost completely filling its lumen, balloting when breathing and prolapsing into the nasal cavity when exhaling.

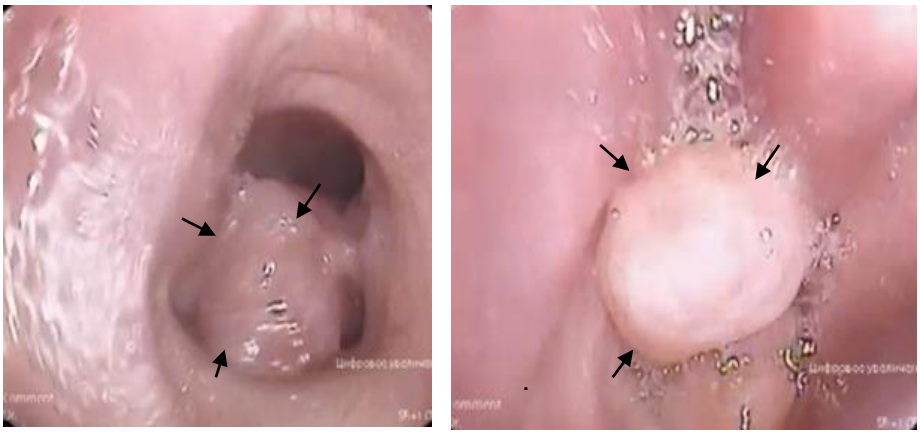

Figure 1. Image of the nasopharyngeal neoplasm (shown by arrows) during transnasal fibroscopy inhalation (a) and exhalation (b).

MRI of the brain with contrast revealed a volumetric mass in the anterior parts of the nasopharynx, rather homogeneous structure, isohypointensive MR signal on T1-, T2-VI, with indistinct, even contours, 17 x 12.5 x 15.5 mm in size. The mass is intimately adjacent to the soft palate, the pharyngeal tonsil, the border between the mass and the described structures being indistinct. The nasopharyngeal lumen at the level of the mass is not seen, the soft palate is pushed downwards causing narrowing of the oral cavity lumen.

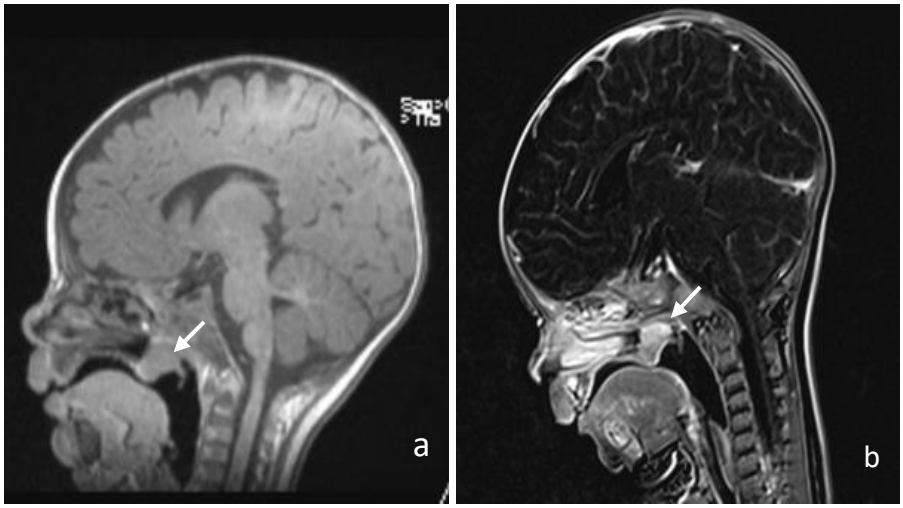

Figure 2. a) CT scan of the head and b) MRI of the brain with enhancement in the sagittal projection. The arrow shows nasopharyngeal neoplasm.

Based on the examinations performed, the child was consulted by an oncologist and the neoplasm was presumed to be benign. After stabilization of the underlying disease, the decision was made to remove the neoplasm in order to restore adequate nasal breathing. Under endotracheal anesthesia with endoscopic control (endoscopes 0° and 70°) after the preliminary soft catheter tying of the soft palate, the nasopharyngeal neoplasm was removed with the help of semiconductor laser with the wave length of 970 nm in a single block (Fig. 3). There was neither bleeding, nor intra- or postoperative complications.

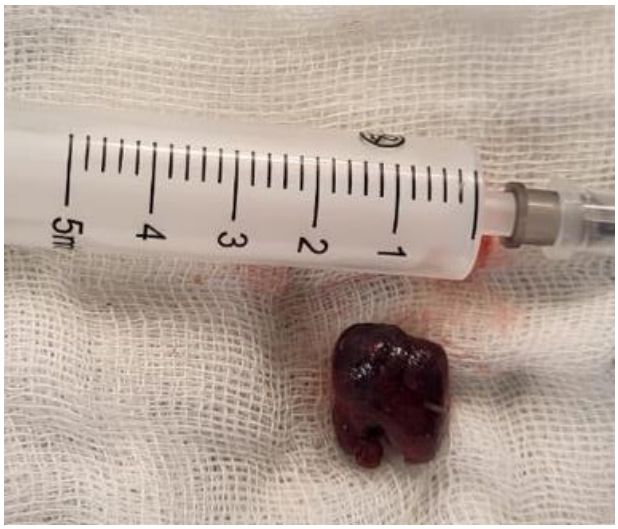

Figure 3. Macroscopic image of the removed nasopharyngeal neoplasm.

The next day after surgery, the child's mother noted a significant improvement in the child's nasal breathing, cessation of dyspnea, and normalization of feeding process. The early postoperative period passed smoothly and the child was discharged to the ENT doctor for outpatient treatment 7 days after surgery.

Histological material obtained for examination demonstrated fragments partially covered with multi-layered squamous epithelium with focal keratinization. A focal growth of granulation high-vascularized tissue of various degrees of maturity with diffuse focal lymphocytic infiltration with a small admixture of neutrophils was found in the superficial parts. The deeper formation has a lobular appearance and biphasic histologic structure: mesenchymal component in the form of intertwining bundles of spindle-shaped cells with round-oval and elongated light nuclei without signs of atypia and mitotic activity, and epithelial component in the form of glandular, trabecular and solid structures consisting of rounded and polygonal cells of glandular type with phenomena of flat cellular metaplasia without atypia, in the lumen of glandular structures positive mucin-exposed secret of various optical density. There were extensive areas of fresh hemorrhages in the stroma with exudative reaction, fibrin deposits, focal petrification, focal fibrosis and mucoidization.

Conclusion: congenital tumor (hamartoma) of the salivary gland rudiment with dyscirculatory changes (fig. 4).

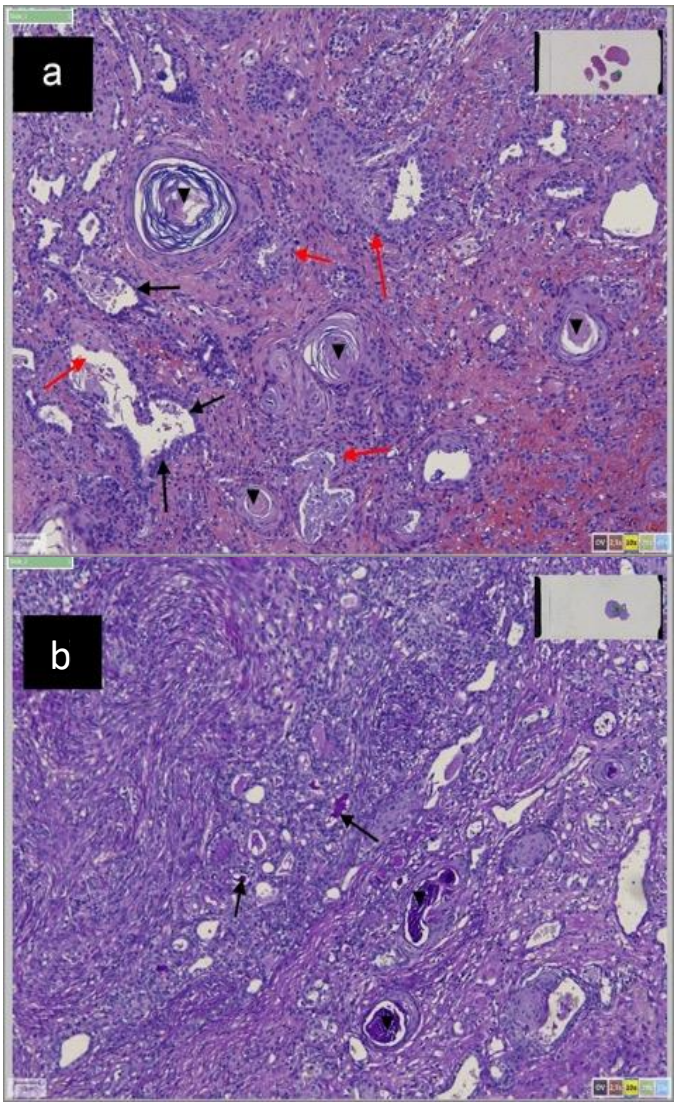

Figure 4. a) Microphotograph shows multiple duct-like structures lined partly by cubic glandular (black arrows), partly by metaplastic multi-layered squamous epithelium (red arrows) with keratinization to the peripheral zones (black triangles). Hematoxylin-eosin staining, x100; b) SHIK-positive kerati-tyne flakes (black triangles) and mucous masses (black arrows) in the lumen of individual dilated ducts can be detected. SHIK reaction, x100.

Control examination of the child 1 month later didn't show any signs of neoplasm recurrence; according to the mother, there were no complaints, the child was active, eating well, there were noticed no signs of apnea, snoring in sleep and obstructive breathing.

Discussion

Nasal breathing disorders in the first 6 months of life can be potentially dangerous as they interfere with feeding, and require careful examination and verification of the cause of nasal obstruction. Respiratory distress syndrome in infants varies widely depending on the area of upper airway obstruction. Volumetric masses in the nasal cavity and nasopharynx in neonates are rare, but their possible presence should always be considered in respiratory distress syndrome in infants during the first months of life [1]. The most common nasal and nasopharyngeal cavity neoplasms are basal cephalocele, nasal cavity glioma (neuroglial heterotopia), and dacryocystocele [2]. Most of these neoplasms in newborn children are benign [3]. Primary and secondary malignant neoplasms of this area are mainly observed in older children, and very rarely

in newborns. They include neuroblastoma, langerhans-cell histiocytosis, rhabdomyosarcoma and lymphoma [4].

The salivary gland anlage tumor (SGAT) in a child presented in our clinical case was first described by Bailie et al. in 1974. [5]. Later, several reports of this neoplasm in children were described in the 1980s and 1990s [6 – 8]. In our country this neoplasm was last time mentioned in publications in 2021 [9]. To date, 42 cases of SGAT have been described in the available publications, and our case is the forty-third one described in the medical literature. Early studies referred to SGAT as a congenital pleomorphic adenoma, suggesting a tumorigenic process [7]. However, later studies deny the tumor nature and present SGAT solely as a benign neoplasm, which dramatically affects its treatment tactics. The absence of destructive changes, morphological similarity to salivary glands, and the absence of recurrence after its radical removal [10 – 12] can prove the benign nature of the process: in the work of Herrmann et al. the postoperative follow-up of a child after removal of SGAT was 5 years [13].

The data analysis shows predominant occurrence of SGAT in males [14, 15]. In most cases, the diagnosis is made in the first months of life, but sometimes SGAT is detected at a later age [16]. Among the leading complaints of children with this neoplasm, prominent is respiratory distress syndrome, i.e., persistent nasal breathing disorders, difficulties in feeding, and slow weight gain. Nasal bleeding is rare. According to the literature, the size of a removed neoplasm varies from 0.5 to 3.5 cm [17].

The main diagnostic methods for suspected nasopharyngeal masses are CT and MRI of the nasal cavity and nasopharynx. These investigations help to determine the connection of a neoplasm with adjacent anatomical structures, absence of intracranial spread, although one case of intracranial spread of SGAT is presented in the literature [18]. Contrast enhancement enables to evaluate blood flow in a neoplasm that is important for planning surgical intervention. Imaging of upper airways is an integral part of diagnostic search for respiratory distress syndrome symptoms, as many specialists focus directly on the evaluation of bronchopulmonary system. For obvious reasons, conservative treatment is ineffective in the case of SGAT.

Endoscopic examination of the nasal cavity and nasopharynx allows visualization of the relation of the nasopharyngeal neoplasm to the surrounding anatomical structures. Thus, the SGAT is characterized by a pedicle location. Total removal of the mass is suggested by the majority of authors (36/42, 85.7%) [15]. Surgery was performed trans-orally, as in our case, or trans-nasally in case of a large mass. Most of the authors did not encounter intense bleeding during the operation.

Histopathologically, SGAT is represented by a combination of benign epithelial and spindle-shaped cells, which form proliferative nodules in the connective tissue stroma. These structures apparently originate from the surface squamous epithelium and are detected in the inter-nodal and per-nodal zones where they merge with stromal-mesenchymal nodules. Some studies have revealed the ultrastructure and immunophenotype of myoepithelium in the latter [19]. In this case, joint expression of epithelial and myogenic immunohistochemical markers confirmed the myoepithelial phenotype of stromal cells. Electron microscopy and immunohistochemistry revealed only epithelial signs in tubular structures and epithelial bands. In this regard, it was suggested that pleomorphic nasopharyngeal adenoma reproduces a salivary gland that develops in the upper respiratory tract [20]. Therefore, in later works, the term "pleomorphic adenoma" was replaced by a “tumor of the salivary gland”. Topographically, the midline location of SGAT is a characteristic feature in comparison with other anomalies in the head and neck region, such as dermoid cyst, nasal glioma, and lingual duct cyst [21]. The fact that no recurrences of SGAT were reported after its removal confirms the benign nature of the neoplasm and its congenital origin (hamartoma).

Conclusions

The described case of the salivary gland anlage tumor in a child is an extremely rare pathology revealed in the first months of life. Symptoms of SGAT are presented predominantly by respiratory distress syndrome, which is a difficulty both in the diagnosis and further management of the patient. Primarily it is conditioned by the age of the patient and nonspecificity of the symptoms: children in the first months of life with symptoms of respiratory distress syndrome are admitted to the pulmonology or infectious diseases department, which in many cases doesn't allow to make a thorough diagnostics and reveal nasopharyngeal neoplasm. Presented clinical case is a typical manifestation of tumor of salivary gland conception - a rare benign nasopharyngeal neoplasm in a child in the first months of life. Early diagnostics including endoscopic examination of the nasopharynx, CT and MRI examinations allowed us to determine the operative treatment tactics, achieve a good functional result in the form of complete relief of

the child's complaints and prevent development of serious complications related to the upper airway obstruction.

Author Contributions: S. Alekseenko—the concept and design of the study, operation and postoperative management. E. Tikhomirova, E. Serikova—collecting and processing of material, provision of materials, writing and editing of the text. S. Barashkova, E. Prodanovich—pathohistologic study of material and processing of material, V. Turieva—processing of material.

Conflict of Interest. The authors declare no conflict of interest.

Funding. There was no funding for this study.

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Article

Assessment of the Correlation of Clinical And Functional Indicators and Cognitive Tests in Patients with Chronic Rhinosinusitis with Polyps.

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Citation: Elizbaryan I., Lazareva L. Assessment of the correlation of clinical and functional indicators and cognitive tests in patients with chronic rhinosinusitis with polyps. Otorhinolaryngology, Head and Neck Pathology (ORLHNP). 2024; 3 (2): 15-23.

https://doi.org/10.59315/ORLHNP.2024-3-2.15-23

Academic Editor: Valentin Popadyuk

Received: 5.06.2024
Revised: 10.06.2024
Accepted:20.06.2024
Published: 12.07.2024

Publisher's Note: International Society for Clinical Physiology and Pathology (ISCPP) stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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Abstract: Relevance: the versatility of the clinical picture of chronic rhinosinusitis with polyps is not limited to nasal obstruction and impaired sense of smell, this disease has a complex complex effect on the central regulatory mechanisms of the patient, manifested by impaired cognitive and mnestic functions of the brain.**Objective:** to evaluate the correlation of indicators characterizing the functional state of the nasal cavity in patients with chronic rhinosinusitis with polyps and cognitive tests in the pre- and postoperative period.**Materials and methods:** testing was performed in 45 patients with chronic rhinosinusitis with polyps with a long history of the disease (M= 117 months). The age of the study group was from 22 to 65 years (M=48.964 years), without concomitant chronic pathology. The scope of clinical testing included testing of synonasal symptoms of SNOT-22, the Lund-Kennedy scale and active anterior rhinomanometry (ml/sec). Changes in X-ray examinations (CT ONP) were assessed on the Lund-MacKay scale. Cognitive abilities were tested on the basis of the MoCA test in points with subsequent interpretation by a psychiatrist. The evaluation of the indicators was carried out before the surgical treatment of chronic rhinosinusitis with polyps, after 1 and 6 months. **Results:** The results were obtained to reduce the indicators of sinonasal symptoms on the SNOT-22 scale from M=31.42 before surgery and up to 4.04 points after 6 months; the Lund-Kennedy scale from M=7.87 to M=0.38 points; the Lund-Mackey scale from M=15.49 to M =0.47 points at the final stage. The indicators of active anterior rhinomanometry tended to increase from M=399.04 ml/sec before surgery and M=856.60 ml/sec after six months. Testing of neurocognitive disorders according to MoHS in patients preoperatively demonstrated average values of 21.49 points, which indicated the presence of mild disorders. Further testing made it possible to obtain indicators of 25.38 points after 1 month, which were fixed with a clear positive trend during the study after 6 months.**Conclusion.** An interdisciplinary approach to the assessment of clinical manifestations in patients with chronic rhinosinusitis with polyps, based on the inclusion of testing of neurocognitive disorders in the study, allows for a more complete assessment of the impact of the pathological process on the patient's body. The inclusion of the MOS test in the complex of pre- and postoperative studies allows us to form an individualized approach to the implementation of therapeutic and rehabilitation measures in this category of patients.

Keywords: polypous rhinosinusitis, chronic rhinosinusitis with polyps, sinonasal symptoms, neurocognitive tests.

Introduction

Chronic rhinosinusitis with nasal polyps (CRSsNP) is a well-studied and complex problem of otorhinolaryngology, which still has a huge number of white spots and still remains an important area in ENT diseases that requires further study [1,2,3]. This is due, on the one hand, to an increase in the number of patients, and, on the other, to the active development of modern treatment and rehabilitation measures based on the latest data in the field of immunology and pathohistochemistry.

The main clinical symptoms of CRSsNP depend on the prevalence of the process and are characterized by nasal breathing disorders, hypo/anosmia, and headache [4]. However, the generally accepted clinical manifestations of chronic productive process in the paranasal sinuses, which in the case of periodic exacerbations is accompanied by purulent-inflammatory manifestations, do not reflect the entire symptom complex of the disease, since they do not take into account the quality of life and other systemic effects on the patient's body as a whole [4,5,6,7].

The diversity of the clinical picture of CRSsNP, depending on the localization and pathomorphology, also includes cognitive and mnestic disorders observed by patients [8,9,10]. In turn, neurologists and psychiatrists have recently been widely discussing the deterioration of cognitive functions against the background of the inflammatory process in the nasal cavity and paranasal sinuses [11, 12, 13]. Surgical treatment to remove nasal obstruction in rhinosinusitis undoubtedly improves the quality of life of patients and allows them to cope with depression [14], improves memory and attention [15], and, in general, significantly affects cognitive abilities [16]. A set of data on the complexity of the complex impact of chronic productive inflammation in the paranasal sinuses formed the basis of the study [17].

Objective: to assess the correlation of indicators characterizing the functional state of the nasal cavity in patients with chronic rhinosinusitis with nasal polyps and cognitive tests in the pre-and postoperative period.

Patients and research methods.

The study included 45 patients with CRSsNP who were treated at the Krasnodar Regional Health Center No. 3 in the period from May 2022 to February 2023. The group of tested patients with CRSsNP was represented by individuals aged from 22 to 65 years (M=48.96 years, σ = 13.137), without concomitant chronic pathology (exclusion criteria-diseases of the cardiovascular system, bronchial asthma, etc.). The duration of the disease in patients was at least one year (M=117 monthsyatsev, from 12 months to 396 months, σ = 117.816). The study included 28 men (62.2%) and 17 women (37.8%). In accordance with the indications, the patients underwent endoscopic polysinusotomy in the required volume [18].

The scope of clinical testing included тестированиеSNOT-22 sinonasal symptom шкалуtesting, Lund-Mackey scale, and active anterior rhinomanometry (ml / sec). Changes in X-ray examinations (CT of paranasal sinuses) were evaluated on the Lund-MacKay scale. Cognitive abilities were tested on the basis of the MoCA test – the Montreal Cognitive Scale – an international screening method for studying cognitive functions that evaluates attention and

concentration, executive functions, memory, speech, opto-spatial activity, conceptual thinking, counting and orientation. The test result was evaluated in points with subsequent interpretation by a psychiatrist (from 30 to 26 points – normal, less than 26 points-mild cognitive impairment) [19]. Patients previously received informed voluntary consent and explained all the stages and methods of the study.

Evaluation of clinical tests in parallel with the results of tests of cognitive disorders was carried out by at the patient's admission to the hospital, 1 month and six months after surgery, X – ray tests-in the preoperative period and after 6 months.

Statistical processing of the obtained data was performed using the Microsoft Excel MSO application software packages (16.0.12026.20312), Statistica 12.5.192.7 (StatSoft, Inc., USA). In order to check the digital data for normality depending on the sample size, chi-square criteria were used. For the normal distribution of data, parametric methods were used: the arithmetic mean (M) was used as descriptive statistics. For statistical analysis, correlation and regression analysis (Pearson coefficient) was used.

Research results

Analysis of sinonasal manifestations of CRSsNP according to the SNOT-22 questionnaire filled in by patients and the Lund-Kennedy scale, based on a point assessment of qualitative indicators, namely, the nasal polyposis process, at the initial stage of the study (before surgery) showed the severity of clinical manifestations in all patients (Table 1).

1 month after the operation, the SNOT-22 questionnaire showed a significant decrease in the values-from M=31.42 points to M=10.04 points, and after 6 months-M=4.04 points. On the Lund-Kennedy scale, a similar trend was observed: before the operation, the average values were M=7.87 points, then after 1 month-M=1.49 points, and at the final stage after 6 months-M=0.38 points.

Indicators of active anterior rhinomanometry showed positive dynamics with M=399.04 ml / sec before surgery, the maximum increase in the first estimated postoperative period was M=778.89 ml / sec. The further trend had the same trend in direction, but at a lower rate with the achievement of up to M=856.60 ml / sec, which can be estimated as close to the norm.

According to the Lund-MacKay scale, the average values in the studied group of patients with CRSsNP were M=15.49 points. Since the X-ray control was carried out after 6 months, the indicators of the final stage were M=0.47 points, which indicated a bright positive dynamic.

Testing of cognitive impairment in patients before surgery showed average values of M=21.49 points, which indicated the presence of mild disorders. Further testing allowed us to get the indicators M=25.38 points and M=26.93 points after 1 month (the norm is more than 26 points), which were fixed after 6 months.

Table 1. Characteristics of functional and clinical parameters and cognitive testing in patients with chronic rhinosinusitis with nasal polyps in the pre-and postoperative period.

Clinical and functional parameters	Mean (M)	Minimum (min)	Maximum (max)	Standard deviation (σ)
Pre-surgery				
Rhinomanometry (ml/sec)	399.04	21.0	627.0	150,174
Lund-Mackey (points)	15.49	5,000	23,000	5,142
Lund-Kennedy (points)	7.87	4,000	10,000	1,646
MoCA test (points)	21.49	17,000	28,000	2,139
SNOT-22 (points)	31.42	12,000	59,000	9.258
1 month after surgery				
Rhinomanometry (ml / sec)	778.89	162,000	1249,000	224,500
Lund-Kennedy (points)	1.49	0.000	4,000	1,180
MoCA test (points)	25.38	22,000	28,000	1,353
SNOT-22 (points)	10.04	2,000	20,000	5,130
5,130 6 months after surgery				
Rhinomanometry (ml/sec856	856,60	.60 314,000	1329,000	221,128
Lund-Mackey (points)	0.47	0.000	2,000	0.815
Lund-Kennedy (points)	0.38	0.000	2,000	0.535
MoCA test (points)	26.93	24,000	30,000	1,304
SNOT-22 (points)	4,04	0,000	15,000	3,411

An additional statistical analysis, with the determination of correlations, allowed us to determine the main parameters that characterize the results of the study in patients with chronic rhinosinusitis with nasal polyps (Table 2).

Table 2. Correlations of clinical and functional parameters in patients with chronic rhinosinusitis with nasal polyps in combination with testing of neurocognitive disorders in pre- and postoperative periods

Study stages														
Clinical and functional parameters and test results	Before surgery					After 1 month from surgery				After 6 months from surgery				
	Rhinomanometry	Lund-Mackey	Lund-Kennedy	MoCA Rhinomanometry	SNOT-22	Rhinomanometry	Lund-Kennedy	MoCA	SNOT-22	Rhinomanometry	SNOT-22 Lund-Mackey	Lund-Kennedy)	MoCA	SNOT-22
Rhinomanometry Test	1	-,411**	-,086	,332*	,158	,624**	-,289*	,132	,148	,693**	-,315*	-,403**	,035	,044
Lund-Mackey	-,411**	1,620	,620**	,444**	,250*	,413**	,297*	-,455**	,053	-,309*	,601**	,444**	,005	-,003
Lund-Kennedy	-,086	,620**	1	-,433**	-,008	,	000[397]**	-,201	-,137	-,027	,251*	,291*	,261*	-,379**
MoCA test	,332*	-,444**	-,433**	1	-,163	-,097	-,196	,696**	-,095	,106	-,043	-,304*	,428**	-,006
SNOT-22	,158	,250*	-,008	-,163	1,188,001	,188	,001	-,541**	,442**	,142	,226	,054	-,482**	,280*

**. The correlation is significant at 0.01 (1-sides).
* . The correlation is significant at the level of 0.05 (1-sides).

According to the obtained results of statistical analysis (tab. 2) it can be observed that active anterior rhinomanometry, as a method for assessing nasal obstruction, showed significant correlations with the Lund-Mackay scale data at the initial stage of the study, and average correlations after 6 months, active anterior rhinomanometry scores were negative preoperatively. After 6 months, a significant correlation was determined. For MoCA test, active anterior rhinomanometry showed a moderate correlation only preoperatively, and no correlation was found at other stages. no correlations were obtained for the SNOT-22 scale. In the postoperative period, for active anterior rhinomanometry, there were significant correlations in the dynamics of changes after 1 month and six months ($p<0.01$).

To assess clinical manifestations based on endoscopic examination (Lund-Kennedy scale), a significant correlation was observed with the data of the Lund-Mackay scale and the MoCA test at the first stage of the study and with SNOT-22 testing after 6 months, but in the opposite direction. A less pronounced correlation, where $p<0.05$, was found for the Lund-Mackay scale and the MoCA test at the final stage of the study. Internal correlations in the Lund-Kennedy scale assessment were assessed as significant and quite naturally reflected the picture of the postoperative period in patients with CRSsNP.

Results of testing the SNOT-22 questionnaire on the clinical manifestations of nasal obstruction in patients with CRSsNP revealed a significant correlation only with the MCA test. At the initial stage of the study, this correlation was average, but then it can be assessed as significant in severity (after 1 month and six months).

The Lund-Mack a y score of radiological changes performed before surgery showed a pronounced one-way correlation at the initial stage, and with all indicators except for the SNOT-22 test, where it was of average significance.

The MoCA test in the study at the initial stage revealed a positive correlation with the data of the SNOT-22 questionnaire, which later acquired the opposite direction. For the indicators of active anterior rhinomanometry, Lund-Mackay and Lund-Kennedy scales, a correlation was recorded only at the first stage of the study. It is noteworthy that there is a significant correlation according to the MoCA test itself in the postoperative period ($p<0.01$).

Discussion of the research results

The improvement of general well-being in patients with CRSsNP after surgical treatment aimed at normalizing or improving nasal breathing is due not only to the elimination of nasal obstruction. The influence of nasal breathing on a whole complex of important systems in the human body is determined physiologically.

The conducted study of a complex of clinical and radiological tests characterizing patients with chronic rhinosinusitis with nasal polyps demonstrated quite natural stages of postoperative recovery. At the initial stage of the study, preoperatively, the tests that characterize nasal obstruction (SNOT-22 and active anterior rhinomanometry) were quite significant, which ultimately, in combination with clinical and radiological indicators, served as the basis for the operation.

The regularity of the fact that in the postoperative period the data of the Lund-Mackay ay (computed tomography data) and Lund-Kennedy (endoscopic assessment of the nasal cavity) scales tended to decrease in the score is quite explicable by the observation period. It is interesting to analyse the correlation of these indicators with the data of the SNOT-22 patient

questionnaire. Only complete recovery of the nasal mucosa after 6 months with the elimination of postoperative oedema was evaluated positively by patients when filling out the questionnaire. For the Lund-Mackey scale, the combination of the pathological process in the SNP with the results of the survey took place only at the initial stage of the study. In the future, no regularities were found for these indicators.

The analysis of the questionnaire survey of patients with CRSsNP on the severity of neurocognitive disorders (MoCA test)is of maximum interest both at the initial stage of the study, and during follow-up in the early and late postoperative period in combination with clinical and functional indicators. Given that cognitive functions include such important components as perception, attention, memory, thinking, praxis and gnosis [20], and are involved in the formation of the second signal system, the importance of their study seems quite relevant.

Studies aimed at diagnosing neurocognitive disorders in the preoperative period in patients with CRSsNP were combined with the severity of nasal obstruction (SNOT-22 questionnaires, active anterior rhinomanometry and Lund-Kennedy scale). This allows us to expand our understanding of the effect of nasal disorders on the activity of the central nervous system. Preoperative testing of neurocognitive disorders by MoCA in patients showed average values of 21.49 points, which indicated the presence of mild variants of disorders. Further testing allowed us to get indicators of 25.38 points after 1 month, which were fixed during the study after 6 months.

Conclusion

For patients with chronic rhinosinusitis with polyps, an integrated approach is important, based not only on the severity of nasal obstruction, but also including data from endoscopic examination of the nasal cavity, radiation diagnostics of pathological changes in the paranasal sinuses. In addition, the brightness of the patient's general perception of the existing disease has a certain value.

An interdisciplinary approach to the assessment of clinical manifestations in patients with chronic rhinosinusitis with polyps, based on the inclusion of neurocognitive disorders in the complex of clinical and functional indicators of testing, allows us to more fully assess the impact of the pathological process on the patient's body. It is possible that such a detailed analysis of the symptom complex of clinical manifestations in this disease will allow us to more fully determine the need for surgical intervention in order to eliminate nasal obstruction.

The inclusion of the MoCA test in the complex of pre-and post-operative studies makes it possible to form an individualized approach to the implementation of therapeutic and rehabilitation measures in this category of patients.

Application of artificial intelligence (remove unnecessary):

The article is written without the use of artificial intelligence technologies.

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

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

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Article

The Effectiveness of Treatment Used for Chronic Periodontitis, Involving Antioxidant Drugs, in Patients With Comorbid Pathologies.

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Citation:Ostrovskaya L.Yu., Osipova Yu.L., Morgunova V.M., Pronina N.S., Ermakova O.V., Artemenko Yu.N., Arinina L.V., Gerasimova T.V., Grigorieva A. S., Domenyuk D.A., Kochkonyan T.S., Ivanyuta O.O. The effectiveness of treatment used for chronic periodontitis, involving antioxidant drugs, in patients with comorbid pathologies.Otorhinolaryngology, Head and Neck Pathology (ORLHNP). 2024; 3 (2): 23-31.

https://doi.org/10.59315/ORLHNP.2024-3-2.24-31

Academic Editor: Valentin Popadyuk

Received: 22.05.2024

Revised: 11.06.2024

Accepted:23.06.2024

Published: 10.07.2024

Publisher's Note: International Society for Clinical Physiology and Pathology (ISCPP) stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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Abstract:

Rationale.Despite the ongoing research and the respectively taken preventive measures, the prevalence of periodontal diseases reveals no tendency towards a decrease. When against a number of somatic diseases (peptic ulcer, diabetes mellitus, etc.), inflammatory and destructive issues affecting periodontium turn even more aggressive, whereas conventional treatment fails to ensure stable long-term remission. Antioxidant drugs, while activating the energy-synthesizing functions of mitochondria, correct disorders in the microcirculation system, as well as they improve the rheological properties of blood, and activate the immune system.**Aim of study.**The study was aimed at producing clinical and lab-data based substantiation of employing antioxidant drugs within comprehensive treatment offered to cases of periodontitis where patients feature a comorbid pathology.**Materials and methods**.The study methods included a clinical and laboratory examination and treatment of 232 patients aged 18-60 whose diagnoses were K25 and K26, and who suffered from chronic periodontitis. The entire pool of patients was broken randomly into groups depending on the treatment offered for chronic periodontitis. In Group I (117 patients), the treatment was carried out following the StAR Clinical Recommendations, whereas Group II (115 patients) had Mexidol antioxidant drug included into the treatment plan. Both groups were given first-

line pharmacotherapeutic support for peptic ulcer disease. The control group were 25 basically healthy individuals.During the study, the oral fluid cytokine content (IL-6, IL-10, IL-12, IL-18), the proliferative activity of gingival epithelial cells (I_{Ki-67}, Iapopt, Ibcl-2) were identified, as well as gingival epithelial cells immune-positive to NO-synthase, endothelin-1 and melatonin were detected both prior to and after treatment. The obtained materials were processed with the EXCEL and STATISTICA 6.0 statistical software packages.**Results.**The comprehensive treatment of periodontitis employed to deal with cases featuring comorbid pathology, where Mexidol was added to the standard mode, resulted in normalized proliferation and apoptosis in gingival epithelial cells, as well as in positive dynamics in the quantitative density of gingival epithelial cells immune-positive to nitric oxide synthase and melatonin; another beneficial effect observed was concentration of the studied cytokines in the oral fluid that persisted after 2 months. However, there was hyperplasia of gum cells immune-positive to endothelin-1 to be seen in both groups of patients suffering from moderate and severe periodontitis..**Conclusion**.Mexidol, introduced into the treatment, allowed bringing down the recurrence rate and maintain periodontitis remission in 90.4% of patients with comorbid pathology.

Keywords: periodontitis, comorbid pathology, antioxidant drugs.

Introduction.

Inflammatory periodontal diseases rate among the leading issues faced by dentistry nowadays. Periodontitis is one of the causes behind connective tissue destruction, bone resorption and the development of periodontal pockets, which often leads to pathological mobility and loss of teeth [1-5].

The wide prevalence of this pathology, its progressive course and the low effectiveness of treatment and preventive measures mean that inflammatory diseases of periodontal tissues are to be viewed as relevant and serious not from both the medical stance, yet also from the social one [6-10].

The diagnosis of periodontal diseases relies on data coming from clinical and X-ray examination, which allows identifying the severity of a disease that has developed already [11-15]. Potential prediction of the disease course would make grounds for getting an idea of the content and scope of treatment measures, and for preventing possible exacerbation of periodontitis. The search for extra diagnostic criteria that would help obtain information concerning the patient's status in terms of belonging to a particular risk group, the disease course and the treatment effectiveness is something reasonable and clinically justifiable [16-22].

97% of patients with periodontal diseases have pathology of internal organs detected in them, this pointing at common pathogenetic links between the health issues [23]. The traditional methods used to treat inflammatory periodontal diseases are aimed at eliminating the microbial factor and imply the control of plaque development, the use of local and general anti-microbial, anti-inflammatory drugs, as well as at improving surgical approaches to eliminating the infection and destruction focus in the periodontium. However, they are not always effective enough and often are not enough to prevent the pathology worsening. Antioxidants and antihypoxants, if used in the comprehensive treatment of inflammatory periodontal diseases combined with gastric ulcer (GU) and duodenal ulcer (DU), present a promising option [24,25].

Recent years have witnessed an antioxidant like Mexidol (3-hydroxy-6-methyl-2-ethylpyridine succinate) – a substance structurally similar to vitamin B6 group compounds –

used successfully in many areas of clinical medicine [26]. The benefits that Mexidol offers include antioxidant, antihypoxic, immunomodulatory and antimicrobial effects [27,28].

Aim of study.

The aim of the study implied clinical and laboratory explanation for the use of antioxidant drugs in comprehensive treatment offered for chronic generalized periodontitis (CGP) in patients with comorbid pathology.

Materials and methods.

In order to carry out the effectiveness assessment for Mexidol introduced into the treatment of periodontitis against GU and DU, the 232 patients were divided into 2 main groups. Group I included 117 patients who were given standard dental treatment subject to the Clinical guidelines for the diagnosis of *Periodontitis*. In Group II (115 patients), Mexidol was added to the treatment plan. The drug in question was used according to the scheme as follows: 2 ml of 5% solution, intramuscular, 1 time a day, as well as applications 2-3 times a day into the periodontal pocket (preparation: open 1 ampoule of the drug to soak the turunda with the solution and to be further placed in the periodontal pocket for 20 minutes). The recommended procedure was brushing the teeth with toothpaste from the *MEXIDOL dent* series (2 times a day for 3-5 minutes). The control group included 25 virtually healthy individuals.

The treatment of patients with peptic ulcer disease relied on the Russian Gastroenterological Association (RGA) clinical recommendations, and included a proton pump inhibitor – Omeprazole (20 mg 2 times a day), as well as two antibacterial drugs: Clarithromycin (500 mg 2 times a day), and Amoxicillin (1 g 2 times a day for 7 days), then – Omeprazole (40 mg/ day for 4-6 weeks).

The clinical diagnosis was given based on the classification of periodontal diseases (1983, rev. in 2001), as well as on ICD-C-3. The GU diagnosis relied on the classical criteria [29] and was set in view of clinical, endoscopic, functional and morphological data.

The inclusion criteria for the patients to join the study were as follows: both sexes; age – 18-60; diagnosed chronic generalized periodontitis against GU and DU in the acute phase; signed protocol of informed consent concerning the purpose and type of the activity to be carried out.

The exclusion criteria were: dental anomalies and deformities; dentition extended defects and pathological erasure; orthodontic appliances; Gu and DU complications (bleeding, perforation); long-term non-scarring gastric ulcer (12+ weeks) and duodenum ulcer (8+ weeks); concomitant diseases affecting the digestive system (chronic pancreatitis, chronic cholecystitis, chronic hepatitis in its acute phase); diabetes mellitus; severe concomitant health issues (myocardial infarction, acute cerebrovascular accident); tumors of any localization; complicated allergy history in relation to drugs to be used through the treatment; the patient's refusal to undergo examination.

To identify gum epithelial cells producing endothelin-1, melatonin and NO-synthase, as well as to study the proliferative activity of cells, an immunohistochemical study was performed using monoclonal mouse antibodies to NO-synthase (1:150, Novocastra), to endothelin-1 (Sigma, St. Louis, USA, titer 1:200), Ki-67 protein (1:100, Novocastra), Bcl-2 anti-apoptotic protein (1:100, Novocastra), rabbit antibodies to melatonin (1:100, CIDtech Res. Comp.). The proliferation index (Ki-67 nuclear label) and the apoptosis index were calculated as the rate (%) of positively colored nuclei of gingival mucosa epithelial cells based on the formula:

Ix (%) = N (x / N (i-heme) x 100, where N is the number of Moser-stained apoptotic nuclei or the number of Ki-67-positive nuclei per 1 sq.mm of the section area; N(i-heme) is the number of cell nuclei stained with hematoxylin on serial a slice at the examination area. Similarly to the apoptosis (Iapopt) and proliferation indices (I_{KI-67}), the Bcl-2 (which is an apoptosis suppressor) label index (Ibcl-2) was identified.

The indices were calculated in 10 view fields on three biopsy sections. The test area used to identify the indices included at least 2,000 cell nuclei. The concentration of IL-6, IL-10, IL-12 and IL-18 in the oral fluid was detected through a solid-phase enzyme immunoassay using a Uniplan enzyme immunoassay analyzer with the following kits: Interleukin-6 and Interleukin-10 (Cytokine, LLC, Russia), Interleukin-18 – IFA – BEST (Vector-Best, CJSC, Russia) and Interleukin-12+p40 (IBL, USA).

The statistical processing of the study results was performed with the EXCEL and STATISTICA 6.0 software package, where the average value and the error of the average were set employing the Student and Mann-Whitney reliability criteria. The study was approved by the Ethics Committee of the Saratov State Medical University.

Results

The effectiveness of the traditional treatment enhanced with Mexidol when dealing with patients suffering from periodontitis of various severity degrees has been proven through the positive dynamics of dental indices (Table 1).

Table 1. Dynamics of periodontium clinical indicators, examination carried out 2 months following treatment

Group of patients		SBI	PMA	OHI-s
Patients with mild CGP against GU	Prior to treatment, n=117	2.21±0.08	50.27±2.14	2.41±0.06
	Group I, n=62	0.62±0.07*	18.25±0.37*	1.38±0.07*
	Group II, n=55	0.30±0.05*#	5.88±0.32*#	1.06±0.06*#
Patients with moderate and severe CGP against GU	Prior to treatment, n=115	2.50±0.08	60.44±2.14	2.62±0.07
	Group I, n=55	0.76±0.08*	20.36±0.48*	1.56±0.08*
	Group II, n=60	0.35±0.07*#	12.24±0.45*#	1.25±0.08*#

Note: * the indicators are significantly different from the values registered prior to treatment; # - the indicators in Group II feature significant differences compared to the values in Group I ($p<0.05$).

According to all the respective index indicators (OHI-s, SBI, PMA), in Week 2 of the treatment and 2 months into the treatment following its start, the indicators in Group II patients were significantly lower than in Group I.

Remission of mild periodontitis in Group II was to be observed in all patients with an average of 9.75±0.26 days, respectively, which is in a shorter time if compared to Group I. Analyzing the postoperative period course following the surgical stage, we are safe to say that the

patients of Group II had pain and collateral tissue edema disappearing on Day 3.2 ± 0.3, whereas their counterparts of Group I featured similar phenomena on Day 4.7 ± 0.3. Healing at the surgical intervention spot in Group II was observed on average following 8.0±0.4 days, while in Group I – after 10.6±0.5 days ($p<0.05$).

An analysis of the regression of subjective and objective symptoms of periodontal diseases revealed that 2 months into the treatment, all the patients suffering from mild periodontitis had their remission remaining. Remission of moderate and severe periodontitis was identified in 95.7% of Group II patients and in 69% of the cases in Group I ($p<0.05$).

To obtain objective information concerning the periodontal tissues status after comprehensive treatment with Mexidol, the cell renewal dynamics was analyzed, as well as that of the status of neuroendocrine and cytokine regulation elements.

The results of morphometric analysis of gingival epithelial cells in Group II helped reveal improved proliferation and gingival epithelial apoptosis, along with positive dynamics in the quantitative density of epithelial cells immune-positive to nitric oxide synthase and melatonin, which could be accounted for by the anti-inflammatory and immunomodulatory effects of Mexidol. Furing that, hyperplasia of gum cells immune-positive to endothelin-1 persisted after treatment in both groups of patients with moderate and severe periodontitis(Table 2).

Table 2. The dynamics of cellular renewal in gingival epithelial cells, examination carried out 2 months following treatment

Group of patients		I $_{Ki-67}$ (%)	I apopt (%)	Ibcl-2 (%)
Virtually healthy individuals, n=25		13.5±0.7	0.52±0.04	2.9±0.3
Patients with mild CGP against GU	Group I, n=62	16.0±1.3	0.58±0.06	3.3±0.5
	Group II, n=55	14.0±0.8	0.47±0.06	3.8±0.5
Patients with moderate and severe CGP against GU	Group I, n=55	23.4±1.5*	0.67±0.05*	10.6±0.8*
	Group II, n=60	12.7±1.2#	0.50±0.04#	6.0±0.5*#

Note: the calculations are offered for 1 sq.mm of gum; *– the indicators reveal significant differences compared with the similar ones in the group including healthy individuals ($p<0.05$); # – indicators in Group II differ significantly from the values in Group I ($p<0.05$).

Analysis of cytokine balance indicators showed that 2 months following the treatment, Group II patients were observed to have improvement in IL-6, IL-10, IL-12 and IL-18 levels in oral fluid (Table 3).

Table 3. Quantitative description of gingival epithelial cells immune-positive to endothelin-1, melatonin and NO-synthase, patients examined 2 months following treatment

Group of patients	NO-synthase-immune-positive cells	Endothelin-1-immune-positive cells	Melatonin-immune-positive cells
Virtually healthy individuals, n=25	4.4±0.7	5.2±0.6	12.5±1.1

Patients with mild CGP against GU	Group I, n=62	5.7±0.6	6.0±0.7	13.2±1.0
	Group II, n=55	6.7±0.9	7.5±0.9	13.7±1.3
Patients with moderate and severe CGP against GU	Group I, n=55	10.3±0.9*	22.4±1.0*	8.2±0.7*
	Group II, n=60	5.5±0.7#	14.0±1.2*#	11.2±0.7#

Note: the calculations are offered for 1 sq.mm of gum; *– the indicators reveal significant differences compared with the similar ones in the group including healthy individuals ($p<0.05$); # – indicators in Group II differ significantly from the values in Group I ($p<0.05$).

Prospective follow-up in patients treated with Mexidol showed 100% of the patients having remission of mild periodontitis persisting after 6 months; for moderate and severe cases the same factor value was 90.4%. Talking of patients receiving conventional therapy, the rate of remission persisting for mild periodontitis cases was 95%, while for moderate and severe cases the rate in question was 58%(Table 4).

Table 4. Oral fluid cytokine content dynamics, patients examined 2 months following treatment

Group of patients		Indicator			
		IL-6, pg/ml	IL-10, pg/ml	IL-12, pg/ml	IL-18, pg/ml
Virtually healthy individuals, n=25		12.60±1.51	7.20±1.02	18.5±1.43	11.32±1.26
Patients with mild CGP against GU	Group I. n=62	16.82±1.57	6.40±0.94	23.5±2.59	12.40±1.43
	Group II. n=55	10.73±1.49	9.37±1.63	17.8±1.68	16.45±2.34
Patients with moderate and severe CGP against GU	Group I. n=55	48.6±4.37*	54.8±4.06*	22.72±2.6	38.3±2.53*
	Group II. n=60	15.4±2.05#	11.7±2.56#	20.82±1.0	14.6±1.64#

Note: * the indicators are significantly different from the values registered for healthy individuals; # - the indicators in Group II feature significant differences compared to the values in Group I ($p<0.05$).

Discussion.

The high clinical efficacy demonstrated by Mexidol introduced into treatment of periodontitis against peptic ulcer disease was associated with positive dynamics in the quantitative density of gingival epithelial cells immune-positive to nitric oxide synthase and melatonin, as well as with improved proliferation and apoptosis of gingival epithelial cells and cytokine content in oral fluid, and this outcome is generally in line with the data reported by other authors [30-32]. The results obtained allow claiming a restored balance between aggression factors and cytoprotective properties of periodontitis, which serves a favorable ground for remission in case of periodontitis.

Conclusion.

Using Mexidol allowed reducing preoperative preparation time down to 9-10 days, as well as arrive at stable remission for cases of moderate and severe periodontitis in 90.4% of the patients featuring comorbid pathology, within 6 months of follow-up.

Conflicts of interest. The author have no conflicts of interest to declare.

Funding. There was no funding for this study.

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