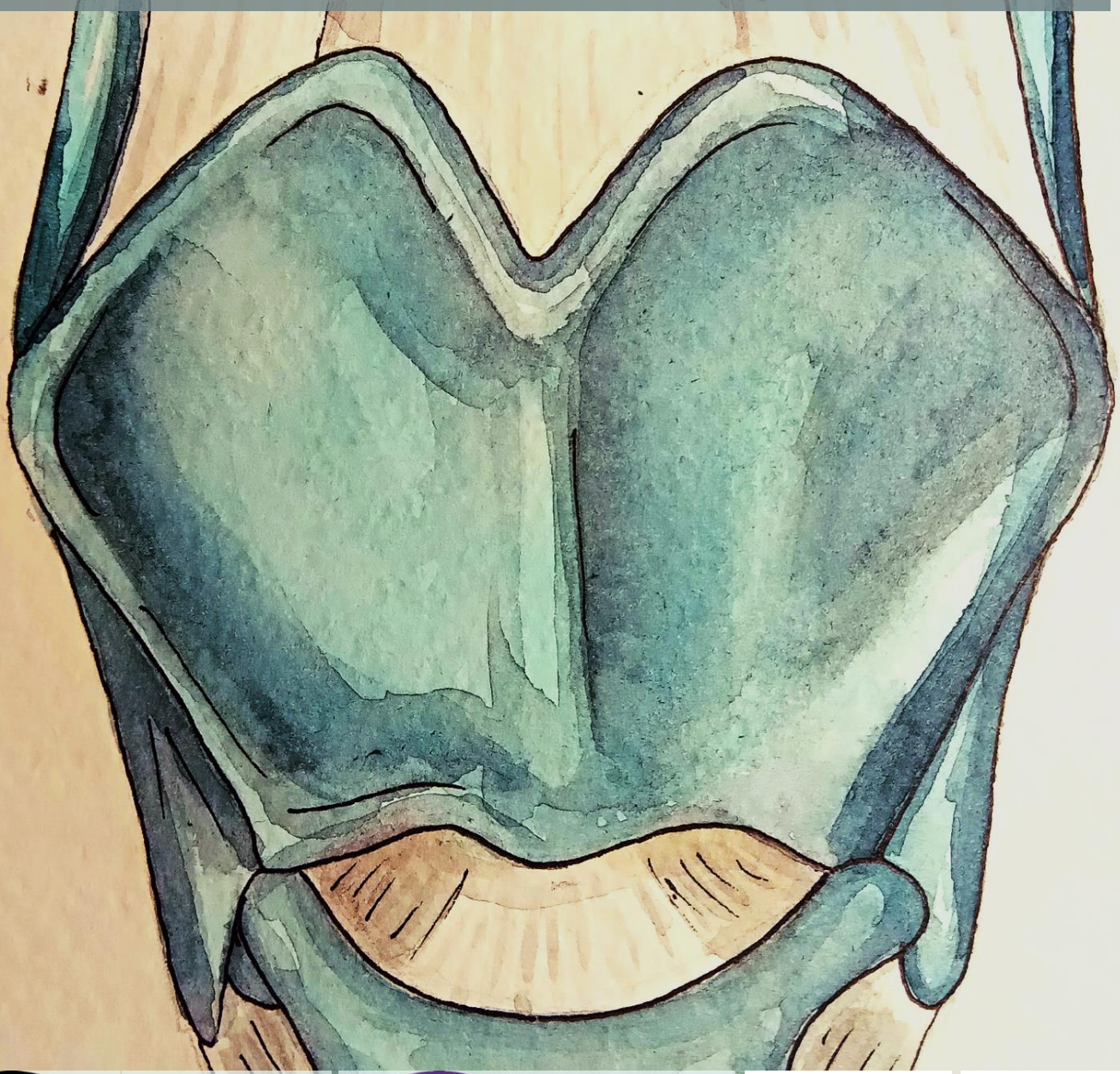
OTORHINOLARYNGOLOGY, HEAD and NECK PATHOLOGY (ORLHNP)

2023 | Vol 2 | N 4 ISSN 2989-1523

Journal of International Society for Clinical Physiology & Pathology



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OTORHINOLARYNGOLOGY, HEAD and NECK PATHOLOGY (ORLHNP)

2023 | Vol 2 | N 4 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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Editor in chief: Valentin Popadyuk DSc, professor,

Editorial staff managers: Polina Mikalskaia Stepan Shilin, Nikita Kuznetsov

Founder and Publisher: International Society for Clinical Physiology & Pathology

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

Article

Study of heart rate and corticosterone variability in the simulation of rhino-surgical interventions in biological objects.

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Citation: Popadyuk V., Kostyaeva M., Kastyro I., Shmaevsky P., Khamidulin G., Dragunova S., Severina E., Yunusov T., Kleyman V., Kuznetsov N., Kazakova O., Tychinskaya D., Kostyuk P., Tsigura D., Ezhova D., Ezhova E. Study of heart rate and corticosterone variability in the simulation of rhino-surgical interventions in biological objects. Otorhinolaryngology, Head and Neck Pathology (ORLHNP). 2023; 2 (4): 4-9.

https://doi.org/10.59315/ORLHNP.2023-2-4.4-9

Academic Editor: Valentin Popadyuk

Received: 13.12.2023
Revised: 20.12.2023
Accepted: 01.01.2024
Published: 30.01.2024

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

Abstract. Aims: to assess changes in the time range of heart rate variability (HRV) and plasma corticosterone concentration in rats after simulating septoplasty. Materials and methods: a septoplasty was simulated in 30 mature male Wistar rats weighing 210-290 g. An ECG was recorded with subsequent analysis of the time domain of HRV, as well as blood sampling for changes in the concentration of corticosterone in the blood plasma. Results: SDNN significantly increased in comparison with the control on days 2 and 3 ($p < 0.001$), but decreased on days 4-5 ($p < 0.001$) and 6 days ($p < 0.01$). rMSSD changed in waves with two irregular peaks on days 1 and 6. SDNN / rMSSD, in comparison with the 1st day of the postoperative period, increased on the 2nd day and continued to grow ($p < 0.05$), and on the 4th day it began to decrease ($p < 0.01$). The total power of HRV was low throughout the postoperative period ($p < 0.001$), except for the 3rd day, when it was equal to the control data. The increase in the total power indicator fell on the 3rd day after the operation ($p < 0.01$), after which its decline occurred again. The concentration of corticosterone in the blood plasma in rats was significantly higher than before ($p < 0.001$). From the 2nd to the 4th postoperative day, its plateau was determined. Conclusion: Simulation of septoplasty leads to changes in the time range of HRV, an increase in the concentration of corticosterone in the blood plasma in rats with its maximum at the time of surgery and after 24 hours, the formation of a "plateau" from the 2nd to the 4th postoperative days, which coincides with changes of HRV.

Keywords: septoplasty, heart rate variability, corticosterone, stress

1. Introduction

The most common surgical intervention for a deviated nasal septum is still septoplasty [1, 2] and can be performed under local or general anesthesia [3]. Using biological models, we have previously shown that modeling septoplasty leads to the development of an anxiety-like state [4] as a result of swelling of the nasal mucosa, inflammatory phenomena [5], and the development of an imbalance in the autonomic nervous system (ANS) [6], which manifested by a change in the behavior of rats in an open field [4]. It was also shown that in this case, the indicators of the frequency range of heart rate variability (HRV), which characterized the shift of the ANS towards sympathicotonia, change [6]. These physiological phenomena were supported by the results of morphological studies of the hippocampus in rats. Thus, after provoking surgical inflammation on the nasal septum, the number of dark neurons and p53-positive neurons increases [7-9]. The importance of studying physiological stress reactions in biological objects is determined by the development of stress reactions and pain syndrome in patients

2. Purpose of the study

Evaluate changes in heart rate variability and corticosterone during modeling of rhinosurgical interventions in biological objects.

3. Materials and methods

3.1. Method of surgical damage:

The study involved modeling septoplasty in 30 mature male Wistar rats weighing 210-290 g. The operation was performed under general anesthesia with a solution of Zoletil 100, which was

injected into the tail vein. After the animal's motor reactions died out, a zigzag scarification of the mucous membrane of the nasal septum was carried out with a metal probe - from bottom to top and from back to front (Fig. 1).

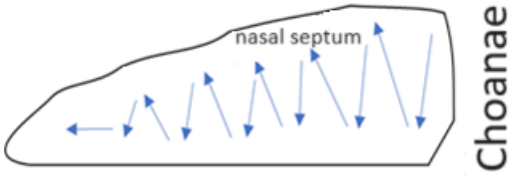

Figure 1. Scheme of modeling of septoplasty in rats - scarification of the nasal mucosa.

3.2. Electrocardiogram and heart rate variability:

Two days before the surgical intervention, all rats, under general anesthesia with a solution of Zoletil 100, were sutured with metal half-rings with capitate ends in three places - two in the back and one in the withers (Fig. 2 a, b). On the day of surgery, before the intervention itself, a control ECG recording was performed for 15 minutes on a Biopac M30-B research polygraph (California, USA). At the same time, the rats were in a free state. After the operation, the ECG was also recorded for 15 minutes daily for 6 days.

Figure 2. Scheme of applying (a) piercing (b) in rats for recording ECG on a Biopac M30-B polygraph (California, USA) (c).

From all recordings, fragments without artifacts were isolated and analyzed in the Biopack student lab 4.1 program. Recording fragments were selected 7.5 minutes (450 seconds) after the start of recording. This was due to the fact that after installing the electrodes, in the first 5-7 minutes the rat on the table got used to them and calmed down. The length of each segment was a minimum of 90 seconds for each rat. The average length of the processed ECG segments was 115±22 s.

Next, heart rate variability was analyzed according to R.M. Baevsky [11] in the Kubios HRV program (Fig. 3). Among the parameters of the HRV temporal spectrum, the following were studied: the standard deviation of R-R intervals (SDNN) between normal QRS complexes, the square root of the sum of squares of the difference in the values of successive pairs of normal R-R intervals (rMSSD), the ratio SDNN/rMSSD and total power (Total power, ms2).

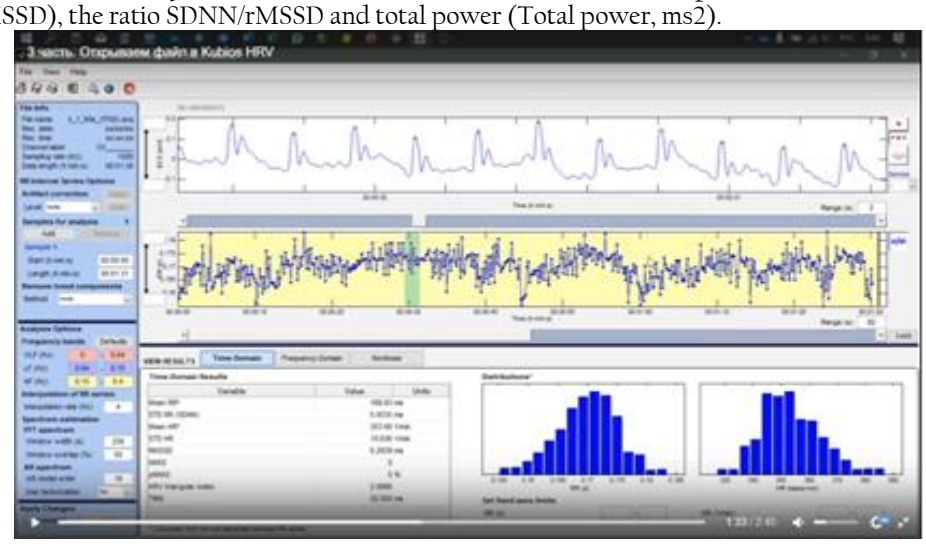

Figure 3. Example of ECG data processing in Kubios HRV.

3.3. Determination of corticosterone concentration

To analyze blood plasma for the concentration of corticosterone in rats, blood was taken after recording an ECG from the tail vein before surgery, at the time of surgery, and 1-6 days after surgery. The blood obtained was immediately centrifuged [12, 13]. Blood samples were immediately centrifuged and plasma was stored at −20°C until analysis. Plasma corticosterone concentrations were quantified using ELISA. A commercial corticosterone enzyme immunoassay kit (Assay Designs Inc., Ann Arbor, Mich., USA) was used according to the manufacturer's instructions.

3.4. Statistical processing of results

Data were processed in Microsoft Exel, MATLAB, STATISTICA 12.6, JASP 0.14.0.0 software. When comparing group data before and after surgery, the Wilcoxon test was used. For each comparison, its own level of significance was determined ($p <$ from 0.001 to 0.05).

4. Results

4.1. Heart rate variability

● Standard deviation of R-R intervals. SDNN significantly increased compared to normal data on days 2 and 3 after septoplasty simulation ($p<0.001$), but decreased on days 4-5 ($p<0.001$) and 6 ($p<0.001$). 01). On days 2-3 of the postoperative period, there was a significant decrease in SDNN compared to day 1 ($p<0.01$). However, on days 4-6 there was a significant decrease ($p<0.001$) compared to the previous observation period (Table 1, Fig. 4a).

● RMSSD. The Wilcoxon test showed that the square root of the sum of the squares of the difference in the values of successive pairs of normal R-R intervals, compared with control data, one day after surgery significantly increased ($p<0.01$), but on the 2nd-5th ($p<0.001$) and on the 6th ($p<0.01$) day it was significantly below normal. The dynamics of changes in rMSSD had a wave-like character with two uneven peaks on days 1 and 6 (Table 1, Fig. 4b). Moreover, on the 4th day its minimum average value was recorded for the entire observation period after modeling septoplasty.

● SDNN/rMSSD. The nature of changes in the average values of this indicator was different from rMSSD. Thus, compared with preoperative values, it was significantly higher on days 2-5 ($p<0.001$), and significantly lower one day after the septoplasty simulation ($p<0.001$). Compared to the 1st day of the postoperative period, on the 2nd day there was an increase in the STDNN/rMSSD ratio ($p<0.001$). On the third day it also continued to increase ($p<0.05$), on the 4th day it decreased ($p<0.01$) compared to the previous day, and continued to significantly decrease only on the 6th day after surgery ($p< 0.05$) (Table 1, Fig. 4c).

● Total HRV power. An assessment of the overall power showed that modeling septoplasty led to a significant decrease in power throughout the entire postoperative period ($p<0.001$), except for the 3rd day, when no significant difference was found compared to the control. The increase in the total power indicator occurred on the 3rd day after surgery ($p<0.01$), after which it decreased again ($p<0.01$) (Table 1, Fig. 4d).

Table 1. Dynamics of changes in time domain parameters and total power of heart rate variability after modeling septoplasty in rats

HRV parameters	Control data	Postoperative period					
		1 day	2 day	3 day	4 day	5 day	6 day
SDNN (ms)	4,76±0,24	4,52±0,25	5,27±0,26	5,1±0,15	4,01±0,26	4,21±0,28	4,41±0,15
rMSSD (ms)	3,96±0,22	4,28±0,34	3,36±0,35	2,94±0,17	2,73±0,25	2,91±0,26	3,41±0,33
SDNN/ rMSSD (ms)	1,2±0,11	1,06±0,11	1,57±0,14	1,73±0,14	1,47±0,13	1,45±0,11	1,29±0,11
Total power (ms2)	27,19±2,95	19,14±2,06	18,49±3,09	24,96±3,23	15,08±3,37	16,75±2,67	18±2,27

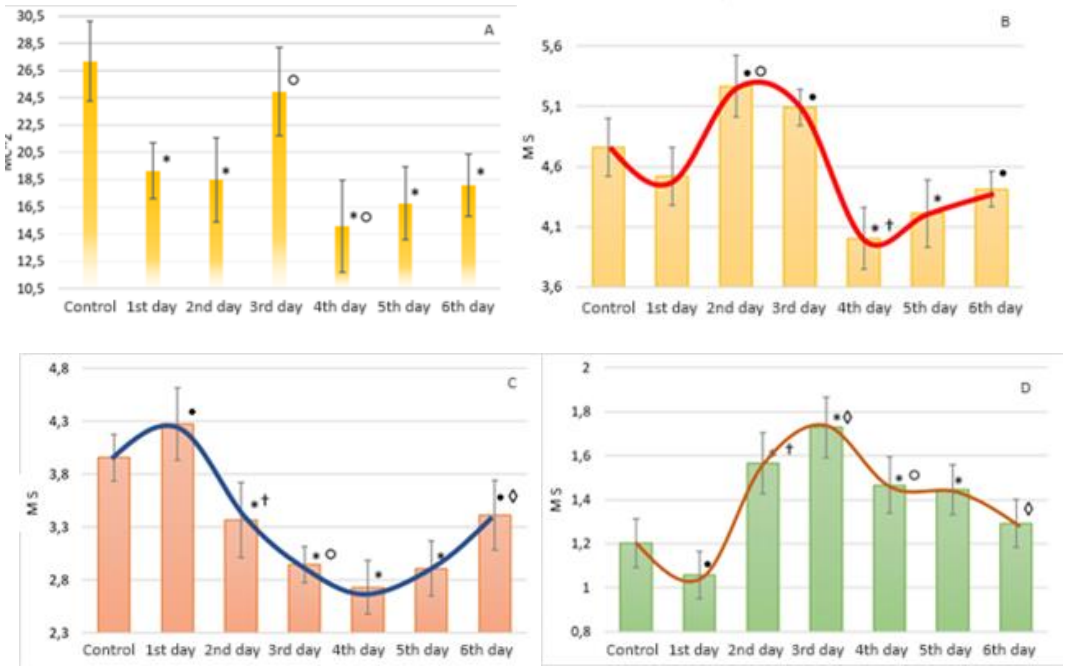

Figure 4. Changes in HRV after modeling septoplasty in the time spectrum: a-standard deviation of R-R intervals (SDNN) between normal QRS complexes; b-rMSSD (the square root of the sum of the squares of the difference in values of consecutive pairs of normal R-R intervals); c – the ratio STDNN/rMSSD; d – total power. Note: * - significant difference between preoperative data (control) and postoperative data at p<0.001; ● - significant difference between preoperative data (control) and postoperative data at p<0.01; † - significant difference between follow – up periods after surgery at p<0.001; o – significant difference between follow-up periods after surgery at p<0.01; ◊ - significant difference between follow-up periods after surgery at p<0.05.

4.2. Corticosterone

According to the Wilcoxon test, at the time of septoplasty modeling and throughout the entire postoperative period, the concentration of corticosterone in the blood plasma of rats was significantly higher than before it (p<0.001). The maximum level of the hormone of the adrenal cortex was noted at the time of the operation itself; a day later its concentration decreased significantly (p<0.001), and from the 2nd to the 4th postoperative day its plateau was determined (Fig. 3.6). But from the 5th day, the concentration of corticosterone in the blood plasma in rats continued to decrease (p<0.01) (Table 2).

Table 2. Corticosterone concentration values in rats after septoplasty simulation.

	control	operation	1 day	2 day	3 day	4 day	5 day	6 day
ng/ml	38,57±2,12	195,77±4,43	159,87±7,89	121,05±6,75	122,55±5,38	118,4±5,7	102,7±5,3	61,7±4,46

5. Discussion.

SDNN represents rapid changes associated with parasympathetic activity. Although SDNN is considered to be a measure of overall HRV power and is sensitive to both sympathetic and parasympathetic input, it is, however, more reflective of parasympathetic tone [14, 15]. Low overall HRV, defined by low SDNN values, reflects decreased parasympathetic and/or increased sympathetic activity [16]. Thus, it was previously shown that an increase in SDNN values corresponded to high activity of the vagus nerve [17]. It is known that SDNN corresponds to the high-frequency component of the HRV frequency domain and characterizes vagal activity [18]. After septoplasty, an increase in SDNN occurred on days 2-3, which corresponded to an increase in plasma corticosterone levels in rats. Consequently, sympathicotonia was observed during this period, since it is known that an increase in the level of glucocorticoids in the blood plasma under conditions of acute or chronic stress occurs against the background of sympathicotonia [19], but against the background of depletion of the sympathoadrenal system under conditions of desynchronosis, its

level may decrease [20]. However, on days 1 and 4-6 after surgery, the power of SDNN was either equal to or lower than control data against the background of a persistent increase in the concentration of corticosterone levels in the blood of animals. It can be concluded that, indeed, both the sympathetic and parasympathetic nervous systems contribute to changes in SDNN, and SDNN in some cases cannot be interpreted unambiguously.

RMSSD characterizes the activity of the parasympathetic division of the ANS [21], and it correlates well with the high-frequency component (HF) of the frequency domain of HRV [22]. In our study, the highest rMSSD values were observed 1 day after surgery, which can be explained by a disruption of normal adaptive processes, since under normal stress conditions the tone of the sympathetic nervous system prevails, along with activation of the hypothalamic-pituitary-adrenal axis [23]. These results are consistent with a drop in the overall power of HRV in the first two days after surgery, which may also indicate a breakdown in adaptive reactions in response to damage to the nasal septum and subsequent sensory deprivation of the peripheral part of the olfactory analyzer [5].

The ratio of SDNN to rMSSD can characterize vagosympathetic balance and is quite consistent with LF/HF (the ratio of the low-frequency component to the high-frequency component of the HRV frequency spectrum or the vagosipathic index) [24]. Moreover, in the absence of differences in SDNN and rMSSD, SDNN/rMSSD may show a difference between study groups [24]. For example, if SDNN/RMSSD is an appropriate expression of LF/HF, higher SDNN/RMSSD, for example in fibromyalgia, compared with healthy controls, characterizes a shift in the balance of the ANS towards the sympathetic component, which is consistent with other studies [25, 26]. Changes in SDNN/rMSSD confirm the idea that on the first day after septoplasty modeling in rats, disadaptation reactions develop, which are manifested by an increase in the activity of the parasympathetic nervous system against the background of an increase in corticosterone, as well as a decrease in the activity of rats in the open field [4, 6], and in the subsequent postoperative period, the body's response to surgical stress is characterized by an increase in the activity of the sympathetic nervous system with an increase in total power in the period 2-4 days, with a peak on the third day, which coincides with the maximum changes in the cytoarchitecture of the pyramidal layer of the hippocampus in almost all of its subfields [7-9], as well as with the formation of a "plateau" on the graph of corticosterone concentration (Fig. 5).

Figure 5. Dynamics of changes in the concentration of corticosterone in blood plasma in rats before and after the simulation of septoplasty. Note: * - significant differences between preoperative data (control) and postoperative data at p<0.001; † - significant difference between postoperative follow-up periods at p<0.001; ‡ – significant difference between postoperative follow-up periods at p<0.01.

6. Conclusions

The concentration of corticosterone in the blood plasma, SDNN/rMSSD and the total power of HRV most accurately characterize the developing responses of the body under conditions of surgical stress when modeling septoplasty in biological objects. Thus, modeling septoplasty in rats leads to the development of disadaptive processes on the first day, followed by normalization of adaptive processes in the period from the second to the fourth postoperative days.

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

Morphofunctional changes in brain and peripheral blood in aged Wistar rats due to AlCl3 exposure

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Abstract: The purpose of the study: To examine morphofunctional changes of brain and peripheral blood in aged Wistar rats to observe adaptive reactions as a response on AlCl3 exposure.
Methods: The work was performed on male Wistar rats, 24 months of age. Animals consumed a solution of AlCl3 100 mg/kg per day for 60 days. Morphological changes of neurons and microglia, mRNA expression levels of pro- and anti-inflammatory cytokines, microglia activation markers, amyloid-related and hypoxia-related proteins, as well as monocyte and lymphocyte subpopulations in peripheral blood, were examined.
Results: AlCl3-treated old rats showed the increasing of hyperchromic neurons in 2 out of 3 examined regions of the hippocampus; morphological features of microglia cells' dystrophy; the upregulation of pro-inflammatory cytokine Il-18 and the downregulation of anti-inflammatory cytokine Il-10, as well as App, Bace1, and Hif-1a; the decreasing of percentage of B-cells, general CD3+ lymphocyte population, including CD4+ T-helpers and CD8+ cytotoxic cells, but the increasing of CD4+/CD8+ ratio in peripheral blood.
Conclusion: AlCl3-treated aged rats demonstrated systemic maladaptation to AlCl3 impact. Unlike adult rodents, aged ones have the background of inflammaging, as well as elderly people. The exposure of AlCl3 could potentially be a replacement of integral cellular and molecular processes accompanying age-related diseases, presenting in most elderly people, as an enhancer of inflammaging and hypoxia. These conditions make this model of neurodegeneration a reliable one to explore the initial mechanisms of such detrimental process, as well as prove aged rats more suitable subjects to perform future researches in this field.

Keywords: aging, inflammaging, neuroinflammation, neurodegeneration, cellular senescence, age-related diseases, animal models, Alzheimer's disease.

Citation: Sentyabreva A., Miroshnichenko E., Tsvetkov I., Kosyreva A. Morphofunctional changes in brain and peripheral blood in aged Wistar rats due to AlCl3 exposure. Otorhinolaryngology, Head and Neck Pathology (ORLHNP). 2023; 2 (4): 10-18.

https://doi.org/10.59315/ORLHNP.2023-2-4.10-18

Academic Editor: Valentin Popadyuk

Received: 13.12.2023
Revised: 20.12.2023
Accepted: 01.01.2024
Published: 30.01.2024

1. Introduction

The stable growing of world's population as well as average lifespan, especially in developed countries, leads to the increasing of age-related diseases' incidence and prevalence, including ones leading to dementia. It is the most prevalent cause of disability globally [1] and its most common cause is neurodegenerative diseases such as Alzheimer's disease (AD). There were more than 55 million patients with dementia worldwide in 2019 [1], and this number will triple in next 30 years. It is a great burden for not only patients, their families, and healthcare workers. It also demands an annual global cost of just over 1 trillion USD on treatment and social support [1]. Among other reasons, this amount of costs is due the absence of any effective treatment for dementia. Existing and approved drugs can only faintly and briefly slow down the symptoms.

The development of new effective treatment approaches is hampered by insufficient data concerning the initial mechanisms of AD pathogenesis. Recent studies showed that it is quite complex process not limited by amyloid deposits alone [2], [3], and 3rd part clinical trial of Lecanemab, an amyloid-antibody based drug, showed questionable efficacy [4]. The role of inflammaging, or chronic age-related low-grade systemic inflammation is one of the most perspective and intensively studying hypotheses of neurodegeneration's initiation so far. It represents a manifestation of senescence-associated secretory phenotype (SASP), which is expressed by senescent cells of aged organisms [5]. Inflammaging is one of risk factors of other age-related diseases development as well, including advanced stage of atherosclerosis, type 2 diabetes mellitus, metabolic syndrome,

etc. At the same time, these very pathological conditions as well some others, like major depressive disorder [6], may contribute in enhancing of its pro-inflammatory background.

Sporadic form of AD, also known as late onset AD (LOAD), begins to manifest with mild cognitive impairment in people of age >60-65 years [7] and belongs to the group of age-related pathologies. However, its modeling is still being conducted mostly on adult rodents, and lots of studies are performed on various lines of transgenic mice, which pathological processes do not exactly correspond with ones leading to neurodegeneration on humans. Among vast variations of AD animal models there are one based on exposure of aluminum compounds. Al3+ ions are capable of increasing the production of reactive oxygen species (ROS). They involve in mitochondrial and DNA damage as well as promoting of pro-inflammatory mediators production and hypoxic condition establishing [8], [9]. All these events are typical for aging as well, which means that experiments on old animals can provide more relevant data due to the cellular senescence presence. Hence, the purpose of this work was to study morphofunctional changes in brain and peripheral blood in aged Wistar rats to observe their adaptive reactions on AlCl3 exposure.

2. Materials and Methods

2.1. Animals and neurodegeneration modelling

The work was performed on aged male Wistar rats 24 months old (n=20). Animals were divided randomly on 2 groups, 10 animals each. Animals were kept in plastic cages (60 x 38 x 18.5 cm) in social groups of 5 animals each with free access to food and water. The temperature in the vivarium room was maintained within 18-22°C, and air humidity was 50-65%. The study was approved by the Bioethical Commission of the Avtsyn Research Institute of Human Morphology of "Petrovsky National Research Centre of Surgery" (Protocol №36 (12) March 28, 2022). All experimental work involving animals was carried out according to directive 2010/63/EU of the European Parliament and of the Council of the EU on the protection of animals used for scientific purposes (Strasbourg, September 22, 2010).

Rats of the experimental group consumed aluminum chloride (AlCl3) in dosage of 100 mg/kg per day for 60 days with drinking water, as described before [10]. Animals of the control group consumed regular drinking water.

2.2. Samples obtaining and histological prepaprations

On the 61st day of the experiment, samples of peripheral blood were obtained under Zoletil (Vibrac Sante Animale) anaesthesia, then animals were euthanized by overdose (15 mg/kg) of Zoletil. The whole brains were fixed in 10% buffered formalin (BioVitrum, Russia) for 24 hours, then dissected at the level of 6.0 mm posterior relative to bregma (each sample of 5 mm thick) [11]. After that, the specimens were dehydrated with ethanol of ascending concentration, cleared with xylene, infiltrated with a histological wax, and embedded in paraffin blocks for further slicing (5 μm thick).

2.3. Morphological study

For morphological study, histological sections of brains were stained according to Nissl's method. The absolute number of neurons in the standard area of the visual field (25000 μm2) and the relative number of hyperchromic and morphologically altered neurons were evaluated on these sections in zones CA1, CA3, and the dentate gyrus of the hippocampus. The pictures were captured with the Leica microscope (DM 2500 Leica Microsystems) on magnification x400.

2.4. Immunohistochemical study

For ICH-P study, frontal histological sections of brains (6.0 mm posterior relative to bregma) were prepared as previously described [9]. Then they were stained with rabbit primary antibodies Iba1 (1:100; P4C288Ra01, Cloud Clone) and secondary HRP Donkey-anti-Rabbit antibody (1:500; 416035, Novex Life Technologies) with additional hematoxylin staining. The pictures were captured with the Leica microscope (DM 2500 Leica Microsystems) on magnification x1600.

2.5. qPCR-RT study

The expression mRNA was assayed by real-time qPCR in tissue fragments of the prefrontal cortex, preserved in IntactRNA solution (Eurogen, Russia) and stored on -20C until studied. The performed analysis included the detection and evaluation of expression levels of pro-inflammatory cytokines (Il-6, Il-18, and Tnf-a), anti-inflammatory cytokines (Il-10 and Tgf-b), microglia M1 (iNos) and M2 (Cd163+) activation markers, amyloid-related proteins (App and Bace1) and hypoxia marker Hif-1a. The levels of all aforementioned mRNA expression relative to GAPDH expression level as a reference were determined using a qPCRmix-HS SYBR (Eurogen, Russia) con-

taining fluorescent intercalating dye SYBR Green I. Amplification with detection and digital analysis of fluorescence in real time was carried out on DT-96 Real-Time PCR Cycler (DNA-Technology JSC, Moscow, Russia) in a standard mode at 95°C for 5 minutes followed by 95°C for 15 seconds, 62°C for 10 seconds + reading and 72°C for 20 seconds ×45.

Table 1. Used primers' sequences (all picked up by on-line soft Primer-BLAST precisely for rat specie).

Primer	Forward sequence	Reverse sequence
GAPDH	GCGAGATCCCGCTAACATCA	CCCTTCCACGATGCCAAAGT
IL-18	GACAAAAGAAACCCGCCTG	ACATCCTTCCATCCTTCACAG
TNF-a	CCACCACGCTCTTCTGTCTA	GCTACGGGCTTGTCACTCG
IL-10	GCCCAGAAATCAAGGAGCAT	TGAGTGTCACGTAGGCTTCTA
TGF-β	CCGCAACAACGCAATCTATG	AGCCCTGTATTCCGTCTCCTT
iNOS	CGCTGGTTTGAAACTTCTCAG	GGCAAGCCATGTCTGTGAC
CD163	TCTTGTGGACTCTGAAGCGA	TCTTAAATGCCAACCCGAGG
APP	TGGATGATCTCCAACCGTG	CGTCGACAGGCTCAACTTC
BACE1	GGGCAGTAGTAATTTTGCAGT	TTCGGAGGTCTCGGTATGT
HIF-1a	TCACAGTCGGACAACCTCAC	TGCTGCAGTAACGTTCCAATTC

2.6. Flow cytometry

The relative numbers of lymphocytes various subpopulations and monocyte were counted using flow cytometry (Beckman Coulter, USA) in peripheral blood. The following antibodies (eBioscience, USA) were used for immune phenotypic analysis: anti-rat CD3-PE for total T-lymphocyte population, anti-rat CD4-FITC for CD3+CD4+ T-helpers, anti-rat CD8-PE-Cy5 for CD3+CD8+ for T-cytotoxic cells, anti-rat CD45R-FITC for CD45R+ B-cells, and anti-rat CD43-PE for CD43+ monocyte. Erythrocytes were lysed with the OptiLyse C solution (eBioscience, USA).

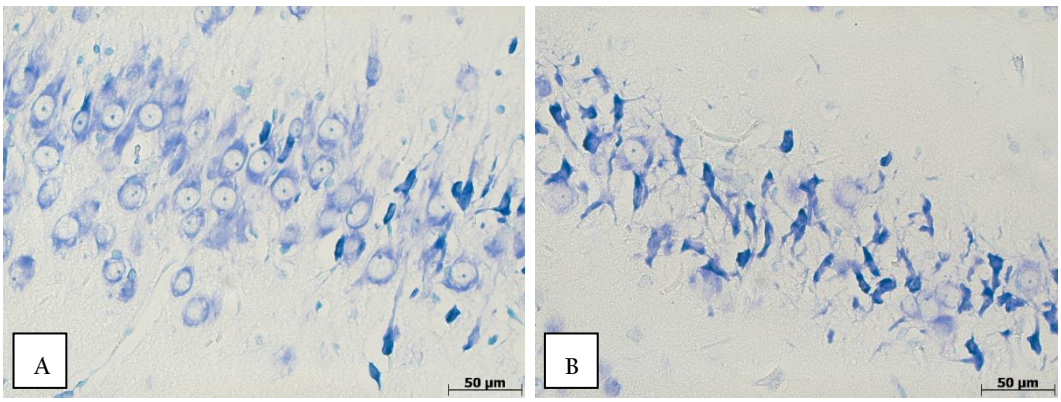
2.7. Statistical analysis.

The results were analyzed by Statistica 8.0 software (StatSoft, Inc.). The normality of data distribution was checked by using the Kolmogorov-Smirnov test. The Mann-Whitney test was used to establish the reliability of differences between groups by median. With $p<0.05$, it was considered as statistically significant.

3. Results

3.1. The percentage of altered hyperchromic neurons

The absolute numbers of neurons in zones CA1, CA3 and the dentate gyrus of the hippocampus were almost the same in both groups, whereas the relative numbers of altered hyperchromic neurons differed significantly. Rats that consumed AlCl3 have shown 2.1-fold number of hyperchromic neurons in CA3 hippocampal zone and 1.7-fold one in the dentate gyrus compared with control group animals (Fig. 1a,b).



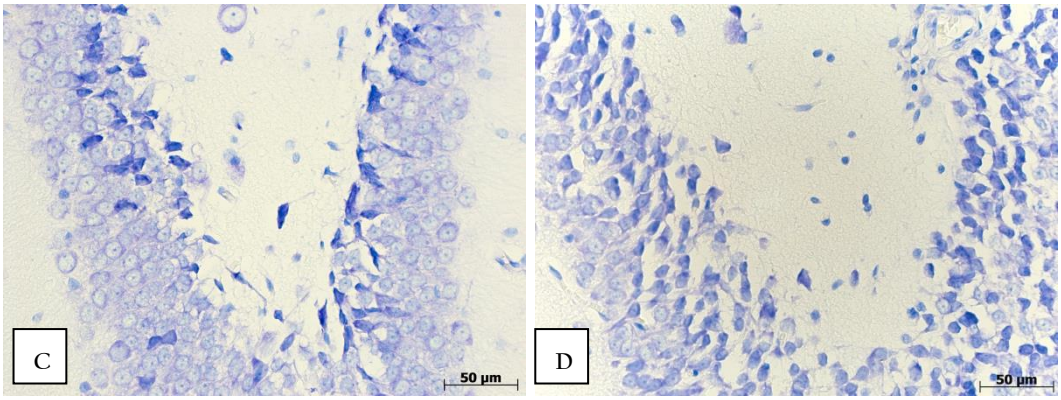


Figure 1a. CA3 zone(A, B) and the dentate gyrus (C, D) of the hippocampus in rats of control (A, C) and experimental (B, D) groups. Nissl's staining, x400.

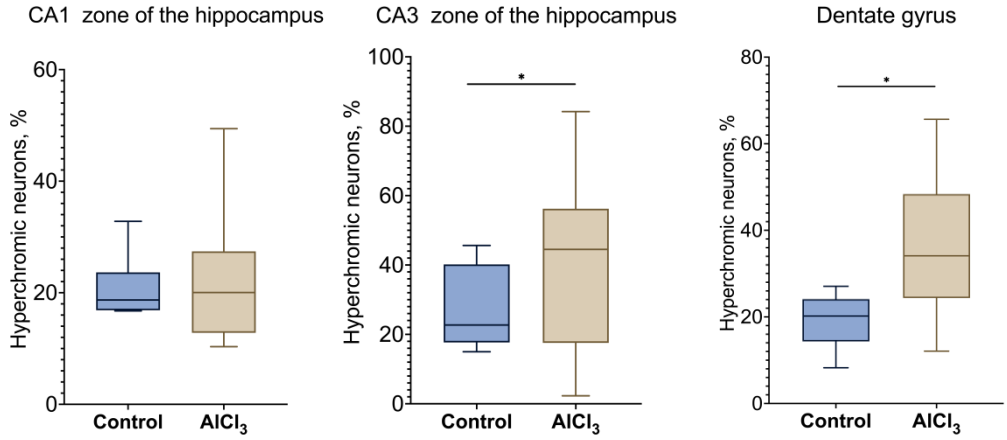


Figure 1b. The percentage of hyperchromic neurons in zones CA1, CA3, and the dentate gyrus of the hippocampus in rats of control and experimental groups.
The data displayed as: line – median, box – 25-75 quartiles, whiskers – non-outlier range;
***** - p<0.05. The Mann-Whitney test comparisons.

3.2. Morphological features of microglia

Identified by ICH staining with anti-Iba1 antibody, in rats of control group microglia cells had an increased size (›30 µm with a reference of 15-30 µm) and spheroidal swelling, hypertrophic, beaded, and tortuous processes. At the same time, there were microglia of an increased size concurrently with beaded, tortuous, and fragmented, but not thickened processes in group of AlCl3-consumed rats (Fig. 2).

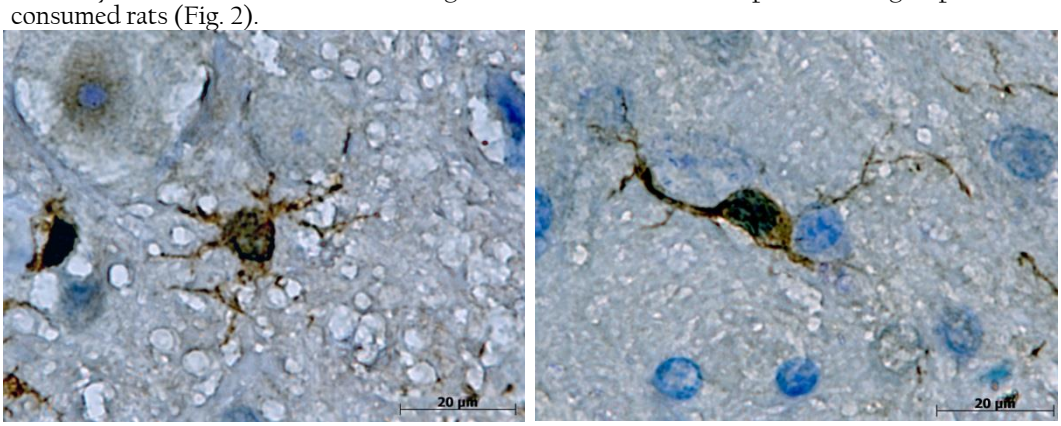


Figure 2. Morphological characteristics of microglia cells with thin and short processes in both Adult-C (A) and Adult-AlCl3 (B) groups, enlarged microglia with spheroidal swelling, hypertrophic, beaded, and tortuous processes in Old-C rats (C), and microglia of an increased size with beaded, tortuous, and fragmented, but

not thickened processes in Old-AlCl3 rats (D). Iba-1 antibody + HRP secondary antibody IHC and hematoxylin staining, x1600.

3.3. qPCR-RT examination of the prefrontal cortex

The result of qPCR-RT of prefrontal cortex tissue fragments demonstrated the statistically significant difference between groups due to Il-18 expression level – it was in 2.8 times less in experimental group rats than in control ones. However, no reliable distinctions were detected in pro-inflammatory cytokine Tnf-α expression levels, as well as in anti-inflammatory Tgf-β ones (Fig. 3). The expression of anti-inflammatory cytokine Il-10 was not detected at all.

The levels of expression of M1 activated microglia marker iNos and M2 activated microglia marker Cd163 were also similar in both groups despite the statistically insignificant tendencies of upregulation of iNos expression and downregulation of Cd163+ one in rats of experimental groups relative to control rodents (Fig. 3).

At the same time, amyloid precursor protein (App) expression was 1.8 times less in rats of experimental group than in control one. Like App, Beta-site APP-cleaving enzyme 1 (Bace1) expression changed in similar way and was downregulated in 2.4 times in rats consumed AlCl3 compared with control group animals. Also, hypoxia-inducible factor 1-alpha (Hif-1a), which displays a presence of a hypoxic condition always appearing alongside inflammation, was downregulated in 4.2 times in experimental group animals in comparison with control ones (Fig. 3.).

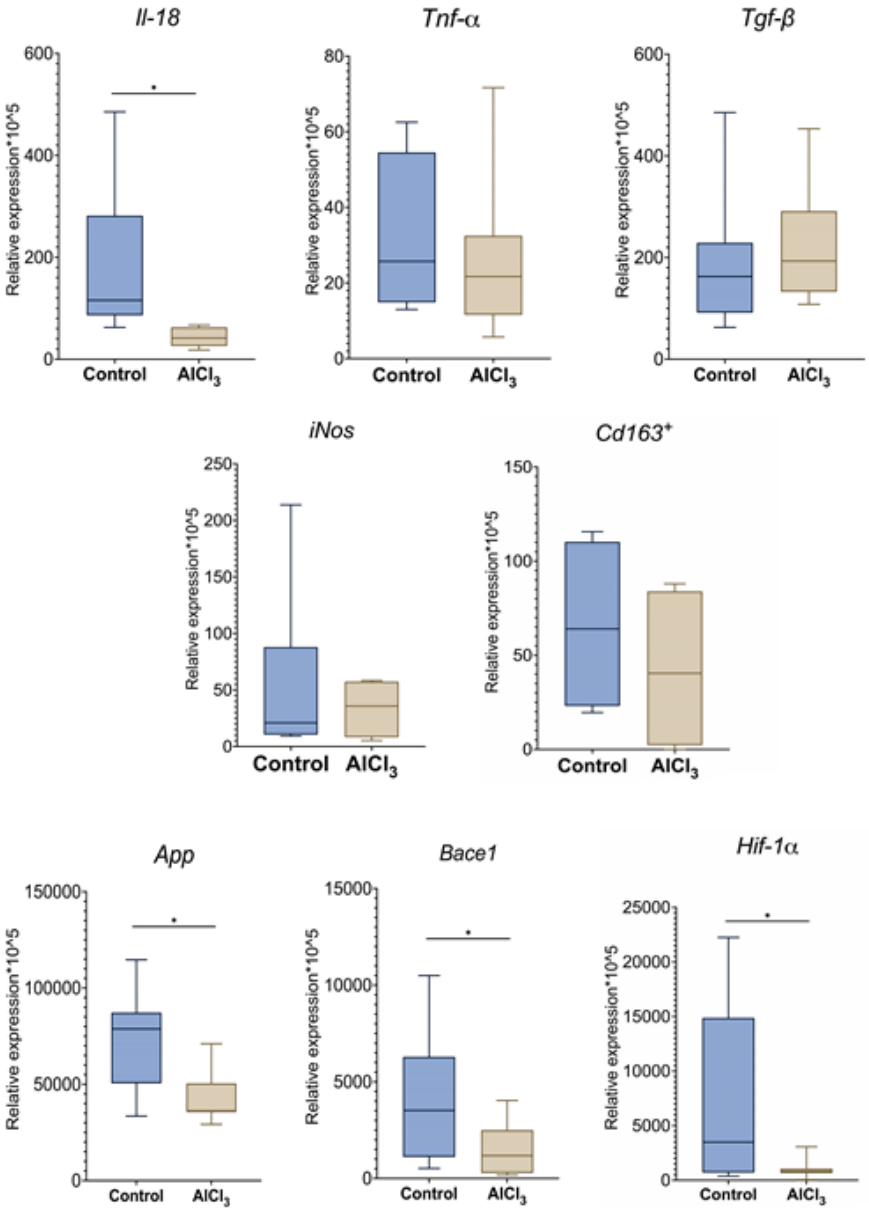


Figure 3. mRNA expression levels of pro-inflammatory cytokines Il-18 and Tnf-α and anti-inflammatory cytokine Tgf-β, microglia activation markers iNos (M1) and Cd163+ (M2), App, Bace1, and Hif-1a in the prefrontal cortex in rats of control and experimental groups.

The data displayed as: line – median, box – 25-75 quartiles, whiskers – non-outlier range;

* - p<0.05. The Mann-Whitney test comparisons.

3.4. Flow cytometry immune phenotypic analysis

The immune phenotypic analysis of lymphocyte subpopulations and monocyte was performed to estimate the impact of AlCl3 on the relative numbers of various immune cells in peripheral blood. Flow cytometry data demonstrated statistically significant differences in the percentage of general CD3+ lymphocyte population as well as CD45R+ B-cells, but not CD43+ monocyte between the observed groups. As for lymphocyte subpopulations, both CD3+CD4+ T-helpers and CD3+CD8+ T-cytotoxic cells decreased in AlCl3-treated rats comparing with control ones, whereas CD4+/CD8+ ratio displayed that the proportion of CD4+ T lymphocyte increased in experimental group rats (Fig. 4).

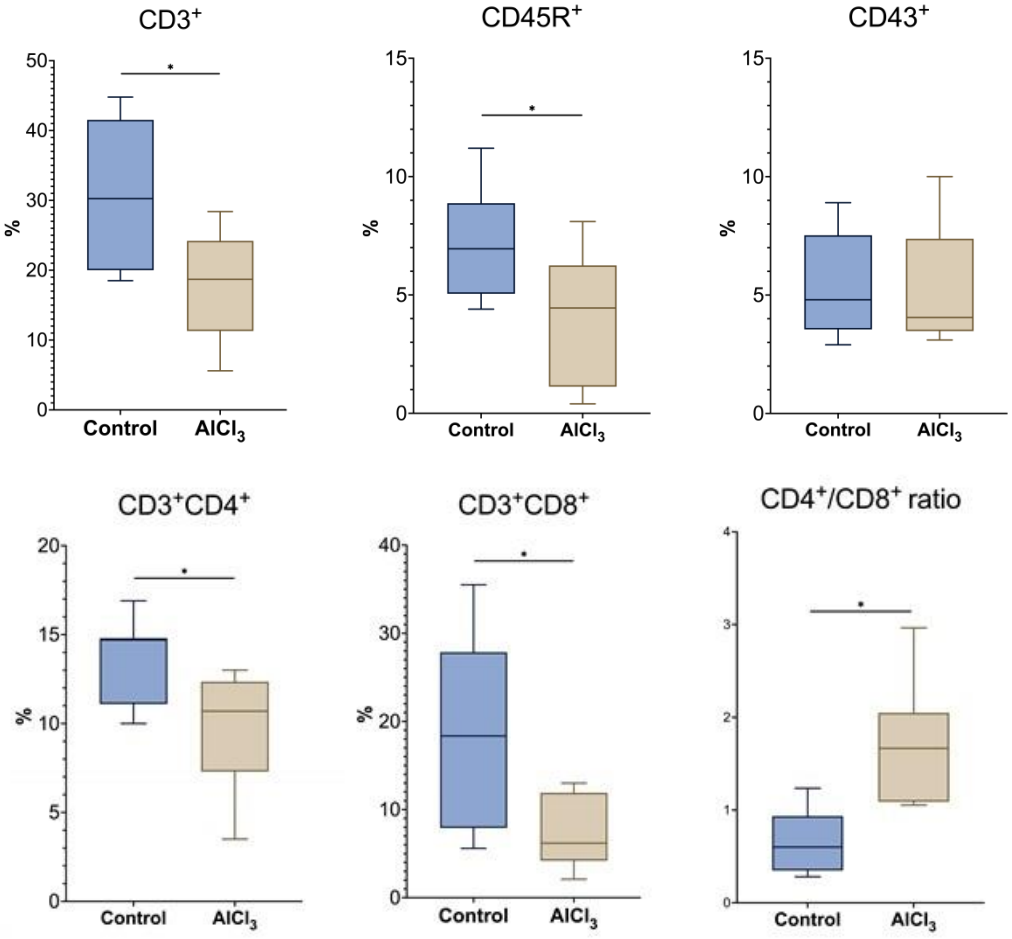


Figure 4. The percentage of general CD3+ T-lymphocyte population, CD45R+ B-cells, and CD43+ monocyte, CD3+CD4+ T-helpers, CD3+CD8+ T-cytotoxic cells, and CD4+/CD8+ ratio in peripheral blood in rats of control and experimental groups.

The data displayed as: line – median, box – 25-75 quartiles, whiskers – non-outlier range;

* - p<0.05. The Mann-Whitney test comparisons.

4. Discussion

The main hallmark of aging is cellular senescence manifesting in the increasing number of SASP-expressed cells. According to our data [15], aged Wistar rats of control group displayed it the same way as it appeared in humans [5]. It makes aged rats a more reliable subject to perform

neurodegeneration modelling due to the presence of pro-inflammatory background of inflammaging, which is absent in adult rodents, including transgenic ones. AlCl3-based models of AD are described widely in literature, including 100 mg/kg dosage giving orally [10], [12], [13], [14], and all these researches were conducted on adult rats and mice. In our previous study, we determined several pivotal morphofunctional distinctions in microglia and immune cells of peripheral blood between groups of adult and old Wistar rats without any external exposure [15]. Now the purpose was to determine and evaluate the response of old rodents on AlCl3.

We detected a notable increasing of the relative number of hyperchromic neurons in CA3 zone and the dentate gyrus of the hippocampus in aged AlCl3-treated rats relative to control ones. We counted mostly morphologically altered neurons of more intense dying, as well as lesser size and polygonal shape, shrunken, and wrinkled. Apparently, neurons with such morphological alterations have ceased to function due to their extinction of interaction with other ones [16], [17]. The reason of more pronounced neuronal damage observed in CA3 zone and the dentate gyrus in comparison with CA1 zone could be probably explained by their different susceptibility to hypoxia. CA1 neurons are presumably more vulnerable to hypoxia and oxygen-glucose deprivation than CA3 and DG [18] probably due to their higher activity [19]. CA1 zone's prime function is the maintaining of short-term memories, whereas CA3 is mostly involved in establishing of spatial and contextual memory [18]. The data concerning the tolerance to hypoxia changing with aging are controversial, although it might increase in advanced age as a result of adaptation processes [20]. However, in case of this particular study, AlCl3 more likely had a direct toxic impact on neurons throughout mitochondrial damage rather than aggravating hypoxic condition.

Unlike aged rats of control group, microglia cells displayed signs of dystrophy in old AlCl3-treated rats instead of activation and/or hypertrophy features. Similar findings were described by Shahidehpour et al. in elder humans, precisely patients with neurodegenerative diseases [21]. Highly likely, it is evidence of their maladaptation due to AlCl3 harmful impact and self-maintaining resources critical shortage in the same way as it occurred in neurons. Such cells are no longer capable of producing enough amounts of export proteins, which are vital for proper functioning, such as immune surveillance and synapse clearance.

The data from experiments conducted on adult AlCl3-treated rats demonstrated upregulation of pro-inflammatory mediator Tnf-a [22], [23] It was also detected in healthy aged rats in comparison with healthy adult ones, whereas the expression level of anti-inflammatory cytokine Tgf-β did the opposite [15]. Meanwhile, we observed no differences in the expression levels of Tnf-α and Tgf-β, as well as in ones of M1 microglia activation marker iNos and M2 microglia activation marker Cd163+ between experimental and control groups. It could probably be explained by dystrophic state of microglia cells, which are both reached the upregulation limits and unable to adapt to malevolent environmental conditions any longer. At the same time, the pronounced downregulation of Il-18 might be caused by neuronal hibernation and death, since they are another source of this mediator [24], [25].

Our data confirms that App and Bace1 expression levels and, therefore, these proteins' subsequent biosynthesis decreased greatly in AlCl3-treated rats relative to control group. It probably displays the advanced stage of neurodegenerative detrimental processes, when neurons are no longer capable of producing APP to form new synapses or maintain deteriorating ones. Therefore, BACE1, which is an enzyme involved in its metabolism, is no longer needed either.

Currently, the data concerning the variability of Hif-1a during the ontogenesis and its impact on age-related genes expression are scarce and controversial. It probably depends on individual hypoxia tolerance and could be both up- or downregulated with aging [20]. However, significant downregulation of Hif-1a in AlCl3-treated rats compared with control ones is likely caused by dystrophy and death of neuron and glial cells as a result of maladaptation to AlCl3 toxic effect.

We observed a statistically significant decline of general CD3+T-lymphocyte population including CD3+CD4+ T-helpers and CD3+CD8+ T-cytotoxic cells in AlCl3-treated rats comparing with control ones. Previously, no difference in there percentage was determined in Wistar rats due to aging alone [15], whereas Zhuang et al. observed its decrease under AlCl3 exposure [26]. However, previous reports [8],[26], [27] observed a decline of CD4+/CD8+ ratio as well, while our data displayed that the proportion of CD4+ T-helpers were higher in AlCl3-treated rats relative to control group. Such discrepance propably might have occured because our experiment was performed on aged rats, whilst previous ones were conducted on adult rodents. Hence, differences in T-lymphocyte population's reactions could vary greatly with aging, but future investigations are warranted.

Unlike relative number of CD3+T-lymphocyte, the decrease of CD45R+ B-cells and CD43+ monocyte percentage was detected in aged humans and rats relative to adult ones [15], [28], [29]. The cause of CD45R+ B-lymphocyte percentage was abated is probably the same as in case of general CD3+T-lymphocyte population, and it is the direct toxic effect of AlCl3. As for CD43+ monocyte, they probably might as express higher resistance to AlCl3 impact; at the same time, they could also decrease both their percentage in peripheral blood and the rate of tissue migration due to inauspicious conditions caused by AlCl3.

5. Conclusions

In regard with all reported data, AlCl3-treated aged rats demonstrated systemic maladaptation to external exposure of AlCl3. With its capability of oxidative stress enhancing, AlCl3 leads to progressive shortage of cell resources and subsequent decline of their functions, already compromised by cellular senescence itself. Unlike adult rodents, aged ones have the background of inflammaging, as elderly people do. Besides, most elderly people have some non-inflectional chronic diseases including age-related ones, such as atherosclerosis, obesity, type 2 diabetes mellitus, etc., whereas rodents do not have them. The exposure of AlCl3 could potentially be a replacement of integral cellular and molecular processes accompanying these diseases as an enhancer of inflammaging and hypoxia. These conditions make this model of neurodegeneration a reliable one to explore the initial mechanisms of such detrimental process, as well as prove aged rats more suitable subjects to perform future researches in this field.

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

Funding: Number of state registration of research, development, and technological work for civil purposes—122030200530-6.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Avtsyn Research Institute of Human Morphology of "Petrovsky National Research Centre of Surgery" (Protocol 36 (12) March 28, 2022).

Informed Consent Statement: Not applicable.

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

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Article

Changes in DOPAC, 3-MT, DOPAC/DA, HVA/DA, 3-MT/DA in the Hippocampus After Simulated Septoplasty and Maxillary Sinusotomy

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Citation: Kostyaeva M., Shalamov K., Korolev A., Kastyro I., Shilin S., Shishkova D., Pinighina I., Mironov N., Inozemtsev A., Popadyuk. V. Changes in DOPAC, 3-MT, DOPAC/DA, HVA/DA, 3-MT/DA in the hippocampus after simulated septoplasty and maxillary sinusotomy. Otorhinolaryngology, Head and Neck Pathology (ORLHNP). 2023; 2 (4): 19-27. https://doi.org/10.59315/ORLHNP.2023-2-4.19-27

Academic Editor: Valentin Popadyuk

Received: 13.12.2023
Revised: 20.12.2023
Accepted: 01.01.2024
Published: 30.01.2024

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

Abstract. *Objective:* to evaluate changes in DOPAC, 3-MT, DOPAC/DA, HVA/DA, 3-MT/DA in the hippocampus after simulation of septoplasty and maxillofacial surgery in rats.

Materials and methods. Simulation of operations was carried out on male Wistar rats under general anesthesia with Zoletil 100 solution. In group 1, septoplasty (n=10) was simulated by the standard method by zigzag scarification of the nasal mucosa. In group 2 (n=10), dental implantation with a titanium implant was performed after the implant bed was formed using drill. In group 3 (n=10), only implant bed was made in the alveolar ridge of the upper jaw without subsequent manipulations. In group 4, 10 rats underwent sinus lifting with bone chips with immediate implantation of a titanium implant. In group 5 (n=10)– with the help of a micro drill through a pre-formed implant bed in the alveolar ridge of the upper jaw, a maxillary sinusotomy was performed with damage to the mucous membrane of the ipsilateral maxillary sinus. Liquid chromatography with electrochemical detection was used to determine the concentration of dopamine (DA), homovanilic acid (HVA), 3,4-dihydroxyphenylacetic acid (DOPAC), 3- methoxytiramine (3-MT) in the hippocampal formation. DOPAC/DA, HVA/DA, 3-MT/DA were also determined.

Results. The concentration of dopamine in the hippocampus, compared with the control, was significantly higher in group 5 and lower in group 4. The HVA concentration was significantly higher in group 2, group 5 ($p<0.01$) and group 1 ($p<0.05$). An intergroup comparison determined that the concentration of HVA was significantly higher in group 2, compared with the rest of the experimental groups ($p<0.001$). In groups 1, 3 and 4, this indicator was significantly lower compared to group 5 ($p<0.01$). The DOPAC level was significantly higher ($p<0.01$) compared to the control data. The concentration of 3-MT was significantly higher in groups 4 and 5 ($p<0.001$), as well as in group 1 ($p<0.05$) and in group 3 ($p<0.01$).

Conclusion. After simulating sinus lifting with immediate implantation and dental implantation complicated by maxillary sinusotomy, there is an increase in the concentration of dopamine metabolites 3-MT, HVA and DOPAC, but at the same time a decrease in dopaminergic activity of the hippocampal formation, compared with simulation of septoplasty and simple damage to the alveolar ridge of the upper jaw. Such changes are markers of disruption of adaptation processes after surgery in the head and neck.

Keywords: septoplasty, hippocampus, dentate gyrus, dopamine, homovanilic acid, DOPAC, 3- MT, DOPAC/DA, HVA/DA, 3-MT/DA.

1. Introduction

Many diseases of the nasal cavity and maxillofacial region require surgical treatment [1-6]: curvature of the nasal septum [2,7], dental implantation [8], sinus lifting [9].

It is known that in addition to the hypothalamic-pituitary-adrenal axis, the hoppocampal formation, including the hippocampus and the dentate gyrus, also participates in the stress response of the body [10]. Previously, it was found that after surgical simulation in the nasal cavity, the body responds with changes in heart rate variability [11], a violation of the normal function of the autonomic nervous system [12], a massive release of gluco- and mineralocorticoids into the blood plasma in the first 2-5 days after surgery [13], as well as changes in the cytoarchitectonics of the pyramidal layer of the hippocampal formation [14]. The hippocampal formation reacts very subtly to external and internal stress factors, for example, monoaminergic systems [15]. Thus, its noradrenergic, serotonergic and dopaminergic systems are particularly sensitive to such effects [16].

Previously, there have been no studies aimed at studying the monaminergic systems of the hippocampus, in particular, dopaminergic, after simulation of surgical interventions in the nasal cavity, upper jaw and paranasal sinuses.

In this regard, the aim of this study was to study the response of the dopaminergic system of the hippocampus in the early postoperative period in response to surgical interventions in the maxillofacial region in rats.

2. Materials and Methods

2.1. Simulation of operations.

The study used male rats of the Wistar line weighing 210-280 g. Surgical interventions in all groups were performed under general anesthesia with the introduction of a solution of Zoletil 100 into the tail vein. In the first group, septoplasty (n=10) was simulated by the standard method by zigzag scarification of the nasal mucosa according to the standard method [13, 17]. In the second group (n=10), dental implantation with a titanium implant was performed after the implant bed was formed using drill (Fig. 1a). In the third group (n=10), only implant bed was made in the alveolar ridge of the upper jaw without subsequent manipulations (Fig. 1b). This group was a comparison group for groups with dental surgical interventions. In the fourth group, 10 rats underwent sinus lifting with bone chips with immediate implantation of a titanium implant (Fig. 1b). In the fifth group (n=10), with the help of a micro drill through a pre–formed implant bed in the alveolar ridge of the upper jaw, maxillary sinus was performed with damage to the mucous membrane of the ipsilateral maxillary sinus (Fig. 1g)

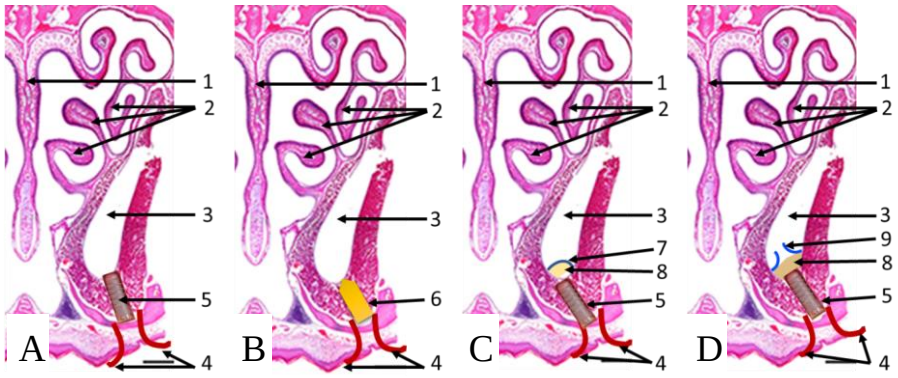

Figure 1. Schemes for simulation of dental implantation (group 2) (A), the formation of implant bed in the alveolar ridge of the upper jaw (group 3) (B), sinus lifting with immediate implantation (group 4) (C) and sinus lifting complicated by maxillary sinusotomy (group 5) (D). Note: 1 – nasal septum; 2 – nasal concha; 3 – maxillary sinus; 4 – mucous-periosteal leaves after incision; 5 – implant; 6 – implant bed; 7 – mucous membrane of the paranasal sinus; 8 – bone chips; 9 – damaged mucous membrane of the paranasal sinus.

2.2. High-performance liquid chromatography with electrochemical detection (HPLC ED).

On the 4th postoperative day after each experimental group animals were euthanized with toxic doses of Zoletil 100 solution, after which the animals underwent guillotining and trepanation of the skull and brain extraction without prior infusion. The obtained samples were homogenized in 1.0 ml of 0.1 n HClO4. with the addition of 250 picomol/ml of the internal standard (3,4-digtdroxybenzyl amine, DHBA) DGBA. The samples were centrifuged at 12,000 g for 10 min on an EPPENDORF 5415R refrigerated centrifuge. The filler liquid in the amount of 20 ml was applied

to the analytical column by direct injection and through the Reodyne7125 injector. Dopamine (DA), homovanilic acid (HVA), 3,4-dihydroxyphenylacetic acid (DOPAC) and 3-methoxytiramine (3-MT, 3-methoxy-4-hydroxyphenethylamine) were separated on a reverse-phase column ReproSil-Pur, ODS-3, 4x100 mm, particle size 3 microns (Dr.Majsch GMBH) using as a mobile phase a citrate-phosphate buffer pH 3.85 containing 0.03 M Na2PO4*2H2O, 0.025M anhydrous citric acid, 0.6 mM sodium octansulfonate, 0.02 mM EDTA and 8% acetonitrile. The determination of monoamines and their metabolites was carried out on a glass-carbon electrode at a potential of +0.85 V against the Ad/AgCl of the reference electrode. The flow rate of the mobile phase was 1.0 ml/min (on an isocratic chromatograph using a GILSON-307 pump (France) and an LC-4B electrochemical detector (Bioanalytical sys., USA).

The samples were registered using the MULTICHROME 1.5 (AMPERSAND) hardware and software complex. All reagents used for the analysis were of a high degree of purity: O.S.C., H.C. or Analytical Grade. To calibrate the chromatograph, mixtures of working standards of the substances to be determined at a concentration of 500 picomol/ml were used.

The concentrations of monoamines in the experimental samples were calculated by the "internal standard" method, based on the ratio of the peak area in the standard mixture and in the sample. All reagents used for the analysis were of a high degree of purity: O.S.C. or analytical grade. The mobile phase was filtered under vacuum before the experiment.

In addition to these substances, the following ratios were calculated: DOPAC/DA, HVA/DA and 3-MT/DA.

The study was conducted in accordance with Directive 2010/63/EU of 22.10. 2010 and Order No. 267 of the Ministry of Health of the Russian Federation of 19.06.2003.

2.3. Statistical analysis.

The data were processed in Microsoft Exel, MATLAB, STATISTICA 12.6, JASP 0.14.0.0 software. When comparing the data of the experimental groups with each other and with the data of the control groups, the Student's criterion or the Mann-Whitney criterion were used. In case of uneven distribution of the sample, the Mann-Whitney criterion was used, in case of its uniform distribution, the Student's criterion was used. For each comparison, its own significance level was determined ($p < 0.001$ to 0.05).

3. Results

3.1. Dopamine.

The Mann-Whitney U-test determined that the level of dopamine concentration in the hippocampus four days after simulation of surgical interventions in the nasal cavity, upper jaw and paranasal sinuses, compared with the control, was significantly higher in group 5 and lower in group 4 ($p<0.001$) (Fig. 2a, Table 1). In group 5, the dopamine level was significantly higher compared to the other experimental groups ($p<0.001$). In Groups 2 and 4, this indicator was significantly lower than in groups 1 and 3 ($p<0.05$), which did not differ statistically from each other ($p<0.001$) (Fig. 2a, Table 1).

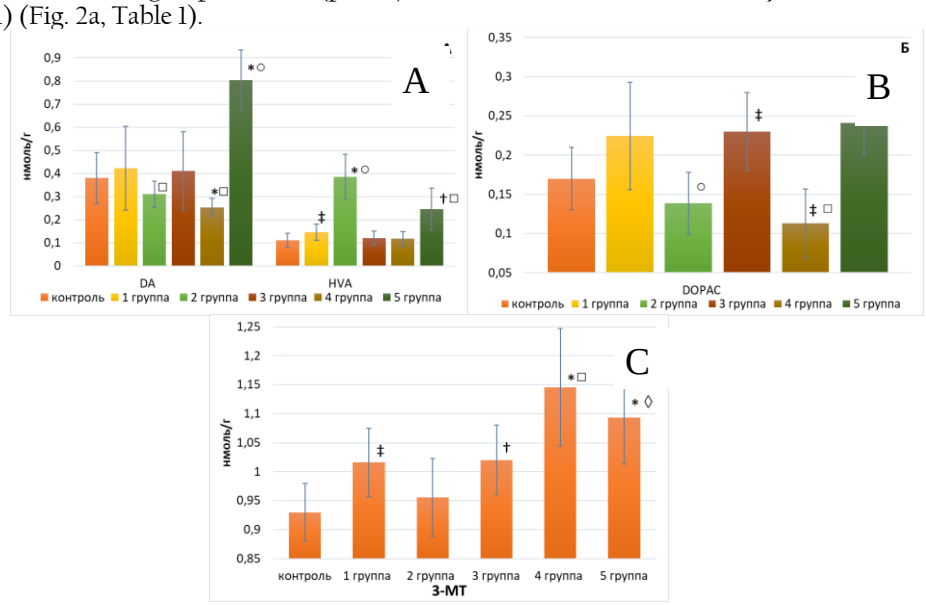

Figure 2. Comparison of the concentrations of dopamine, homovanilic acid (HVA) (A), 3,4-dihydroxyphenylacetic acid (DOPAC) (B) and 3-methoxytiramine (3-MT) (C) in the hippocam-

pus of rats between experimental and control groups. Note: * – a significantly significant difference when comparing experimental groups and a control group at p<0.001; † – a significantly significant difference when comparing experimental groups and a control group at p<0.01; ‡ – a significantly significant difference when comparing experimental groups and a control group at p<0.05; o – a significantly significant difference when comparing experimental groups at p<0.001; o – a significantly significant difference when comparing experimental groups at p<0.01; ◊ – a significantly significant difference when comparing experimental groups at p<0.05.

3.2. HVA.

Evaluation of the concentration of homovanilinic acid in the hippocampus after surgical interventions on day 4 using the Mann-Whitney U-test showed that its concentration was significantly higher in group 2, group 5 (p<0.01) and group 1 (p<0.05) (Fig. 2a, Table 1). An intergroup comparison determined that the concentration of HVA was significantly higher in Group 2, compared with the rest of the experimental groups (p<0.001). In groups 1, 3 and 4, this indicator was significantly lower compared to Group 5 (p<0.01) (Fig. 2a, Table 1). 3.3. HVA.

3.3. DOPAC.

The Mann-Whitney U-test showed that the concentrations of 3,4-dihydroxyphenylacetic acid in groups 3 (p<0.05) and 5 were significantly higher (p<0.01) compared with the control data. The remaining experimental groups did not differ from the control group (Fig. 2b, Table 1).

The level of DOPAC in the hippocampus after simulation of surgical interventions was significantly lower in Group 2 (p<0.001) and in group 4 (p<0.01), compared with the rest of the experimental groups (Fig. 2b, Table 1).

3.4. 3-MT.

Analysis of the content of 3-methoxytiramine in the hippocampus in rats using the Mann-Whitney U-test showed that group 2 did not significantly differ from the control data. The concentration of 3-MT was significantly higher in groups 4 and 5 (p<0.001), as well as in group 1 (p<0.05) and group 3 (p<0.01) (Fig. 2b, Table 1). An intergroup comparison of the concentration of 3-MT revealed that its level was significantly higher in the 4th (p<0.01) and 5th groups (p<0.05), compared with the rest (Fig. 2b, Table 1).

3.5. The DOPAC/DA ratio.

The Mann-Whitney U-test showed that the DOPAC/DA ratio was significantly lower in groups 2 and 4, compared with the control (p<0.001), and this was also noted in group 5 (p<0.01). The remaining experimental groups did not differ from the control group (Fig. 3a, Table 1).

A comparison of the DOPAC/DA ratio between the experimental groups revealed the following. Thus, this indicator in the 2nd and 4th groups was significantly lower than in the 1st and 3rd groups (p<0.001). In the 5th group, this ratio was statistically lower compared to the 1st and 3rd experimental groups (p<0.01), but higher than in the 2nd (p<0.01) and 4th groups (p<0.05) (Fig. 3a, Table 1).

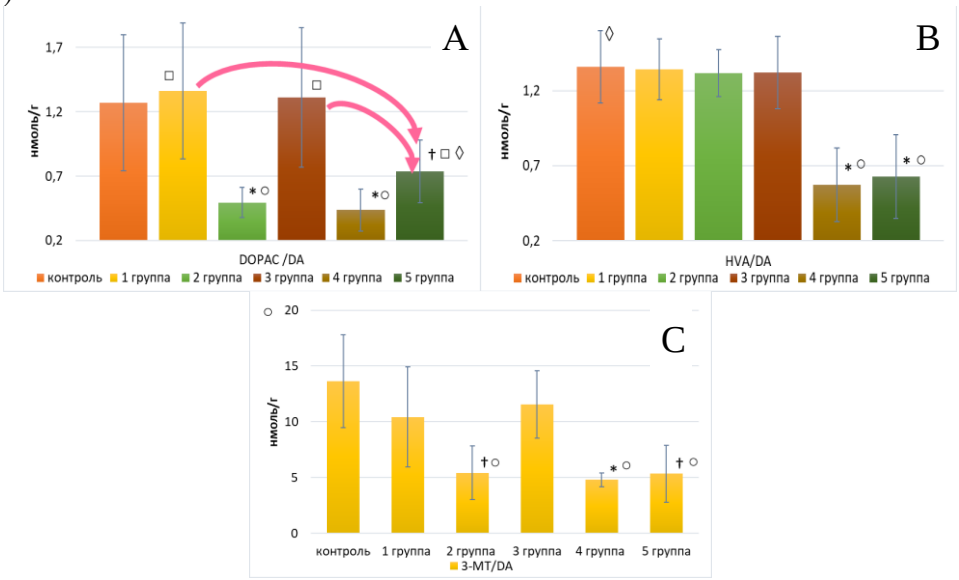

Figure 3. Comparison of DOPAC/DA (A), 3HVA/DA (B) and 3-MT/DA (C) ratios in rat hippocampus between experimental and control groups. Note: * – a reliably significant difference

when comparing experimental groups and a control group at p<0.001; † – a reliably significant difference when comparing experimental groups and a control group at p<0.01; ‡ – a reliably significant difference when comparing experimental groups and a control group at p<0.05; o – a reliably significant difference when comparing experimental groups at p<0.001; – a reliably significant difference when comparing experimental groups at p<0.01; ◊ – a reliably significant difference when comparing experimental groups at p<0.05. Pink arrows – explanations in the text

3.6. HVA/DA ratio.

Evaluation of changes in the ratio of homovanilinic acid to dopamine using the Mann-Whitney U-test showed that, compared with the control group of animals, it was significantly lower in groups 4 and 5 (p<0.001). The remaining groups did not differ from the control (p<0.001) (p<0.001) (p<0.001) (p<0.001) (Fig. 3b, Table 1).

The same was observed when comparing the experimental groups. Thus, the 4th and 5th groups had this ratio significantly lower than in the other experimental groups (p<0.001), which did not differ from each other (Fig. 3b, Table 1).

3.7. The ratio is 3-MT/DA.

The Mann-Whitney U-test determined that in groups 2 and 5 (p<0.01), as well as in group 4 (p<0.001), the ratio of 3-MT/DA was statistically lower than in the control group. The remaining groups did not differ from the control values (Fig. 3b, Table 1). Intergroup analysis using the Mann-Whitney criterion showed that in the hippocampus of rats from groups 1 and 3, the ratio of 3-MT/DA was significantly higher than in the animals of the other experimental groups (p<0.001) (Fig. 3b, Table 1).

Table 1. Indicators of the dopaminergic system of the hippocampus after simulation of rhinosurgical interventions and operations on the upper jaw.

	DA	3-MT	HVA	DOPAC	DOPAC /DA	3-MT /DA	HVA /DA
Control	0,38±0,11	0,93±0,05	0,11±0,03	0,17±0,04	1,27±0,52	13,63±4,16	1,36±0,6
Group 1 (septoplasty)	0,42±0,18	1,01±0,05	0,14±0,03	0,22±0,06	1,36±0,52	10,44±4,49	1,34±0,57
Group 2 (dental implantation)	0,31±0,05	0,95±0,06	0,38±0,09	0,13±0,03	0,49±0,11	5,42±2,39	1,31±0,55
Group 3 (implant bed)	0,41±0,17	1,02±0,06	0,12±0,03	0,23±0,05	1,31±0,54	11,56±3,01	1,32±0,52
Group 4 (sinuslift.+dental implantation)	0,25±0,03	1,14±0,1	0,11±0,02	0,11±0,04	0,4±0,16	4,8±0,63	0,57±0,18
Group 5 (maxillary sinusotomy through the central implant bed)	0,8±0,13	1,09±0,08	0,24±0,09	0,24±0,09	0,73±0,24	5,35±2,56	0,62±0,16

4. Discussion

Under the action of monoamine oxidase (MAO), 3-MT is reduced to HVA and excreted in the urine [18]. The dopaminergic system may be involved in reducing aggressive behavior. Activation of dopamine receptors mediates aggressive behavior, which is caused by electrical stimulation of the hypothalamus [19]. In addition, D2 receptor antagonists weaken aggressive behavior caused by social isolation (SI) [20]. DA is catalyzed to DOPAC by MAO-B, then DOPAC is catalyzed by catechol-O-methyltransferase (COMT) to HVA. However, phytotherapy did not increase the activity of MAO-B in the hypothalamus, which suggests that the HVA content was not associated with an increase in MAO-B activity, and the levels of COMT mRNA were increased as a result of exposure to SI [21]. Other studies have reported elevated levels of COMT in mice that showed aggressive behavior [22]. Since COMT is localized in postsynaptic neurons, an increase in COMT mRNA may be a neuroadaptive response to increased and sustained dopaminergic tone [23].

External stress factors invariably lead to adaptive changes in neurons, which induce sensitization to stress due to a violation of the regulation of dopaminergic and/or noradrenergic systems with activated HVA and cortical response [24].

DA is metabolized by monoamine oxidase to the biogenic aldehyde 3,4-dihydroxyphenyl acetaldehyde (DOPAL) before detoxification by several aldehyde dehydrogenase enzymes to 3,4-dihydroxyphenylacetic acid (DOPAC) [25]. DA and DOPAC modify proteins by self-oxidation of the catechin part to the radical semiquinone or orthoquinone and subsequent addition of Michael to thiols (for example, cysteine) [26, 27]. Similarly, DOPAL can also undergo auto-oxidation of its catechol. It is believed that this self-oxidation increases the reactivity of its aldehyde component [28]. DOPAL also inhibits tyrosine hydroxylase, an enzyme that limits the rate of DA synthesis [29, 30].

It was shown that the concentrations of striatal DA and DA DOPAC and HVA metabolites were significantly reduced in rats injected with 6-OHDA. Tyrosine hydroxylase (TG) is an enzyme that limits the rate of dopamine synthesis, and is mainly expressed in dopamine neurons. Thus, a significantly reduced level of TG protein in the striatum, detected by Western blotting, may reflect damage to the endings of striar neurons and/or death of neurons in SNpc [31]. In another study, it was also shown that a decrease in the level of DOPAC in the cerebrospinal fluid is not only an indicator of Alzheimer's disease, but also a violation of the function of the autonomic nervous system [32]. On the other hand, with post-traumatic stress disorder in the hippocampus, the DOPAC level increases, coinciding with hyperactivation of the noradrenergic system [33].

Extrapolating these data to the present study, it can be assumed that the decrease in the level of DOPAC and the growth of p53-positive neurons, as well as an increase in apoptosis of neurons, in all subfields of the hippocampus are interconnected and may indicate a high level of exposure to sinus-lifting surgery with immediate dental implantation. An increase in the level of DOPAC, compared with the control, was noted in the groups of septoplasty, implant bed and maxillary sinusotomy through the implant bed.

Tissue 3-methoxytiramine (3-MT) accumulated within 10 minutes after monoamine oxidase inhibition can be used as an indicator of terminal dopamine release [34, 35]. Especially its concentration increases with damage to the ventral hippocampus in rats [35].

There is consistent evidence that the release of dopamine acid in the prefrontal cortex during stress suppresses subcortical release of dopamine [36].

Using a microwave fixation system, a significant decrease in DA, 3-MT and HVA was found in the striatum of R6/2 mice aged 8 and 12 weeks, parallel to the motor deficit in these mice [37, 38]. Some of the dopaminergic changes were also observed in areas unrelated to the striatum, such as the hippocampus and frontal cortex, which highlights the early aberrant connectivity of dysfunctional frontal striatum circuits in Huntington's disease [37]. Similarly, several studies have reported a decrease in the level of HVA in cerebrospinal fluid in patients with Huntington's disease prior to the identification of the HTT gene [39]. A decrease in the ratio of 3-MT/DA and HVA/DA in the context of a decrease in DA levels [40] is consistent with more direct measurements of a decrease in dopamine release [41- 42].

It is known that DA plays an important role in the functioning of the central nervous system, influencing various manifestations of mental activity of animals and humans [43]. It has been shown that brain processes involving DA are significantly disrupted during the development of depression [44].

The introduction of dopamine receptor agonists and antagonists into the hippocampus, respectively, improves and worsens hippocampal-dependent learning (45, 46). This fact can be applied to the present study in the context that a significant release of dopamine may indicate a large surgical alteration, provoking a cascade of adaptive reactions that can be aimed at improving the behavior and memory of an animal under stress.

The greatest increase in 3-MT was observed in groups 1, 3, 4 and 5, compared with the control. Considering that in DA it is metabolized in 3-MT and DOPAC in different ways with the help of COMT and MOA enzymes, respectively, it can be assumed that a higher level of dopamine cleavage to 3-MT was observed in all groups except the dental implantation group. An increase in DA metabolism along the DOPA pathway was noted only in the groups of septoplasty, sinus-lifting with dental implantation and complicated sinus-lifting with maxillotomy. It can be concluded that the release of dopamine in the hippocampus, as a neurotransmitter acting on D1/D5 dopamine receptors and inducing long-term potentiation of pyramidal neurons of the CA1 subfield under afferent stimulus from the Shaffer collaterals, can be considered as a defense mechanism (potentiation, improvement of learning and memory) under surgical stress, on the one hand, and the manifestation of inadequate hyperimpulsation into the hippocampus region with an increase in disadoptation reactions, on the other hand [47].

The HVA/DA, DOPAC/DA relationships may reflect the activity of pre-familergic brain activity [48].

Chronic stress is associated with increased levels of norepinephrine (amygdala and hippocampus) and dopamine (HVA/DA, DOPAC/DA) in the prefrontal cortex [49, 50]. Thus, chronic

stress provokes a decrease in HVA/DA, DOPAC/DA. In another study, using the example of chronic stress in rats, it was shown that DOPAC levels in the frontal cortex and in the hippocampus increased, in addition, an increased ratio of 5-HIAA/5-HT was observed in the hippocampus. In the hypothalamus, HVA and DOPAC levels were reduced, as well as the DOPAC/DA ratio. Chronic stress caused a decrease in the mass of the adrenal glands. It has been found that chronic variable stress causes a decrease in dopaminergic neurotransmission in the hypothalamus. Elevated levels of dopamine metabolites in the cortex and hippocampus were also observed [51]. During handling in male rats, the level of DA of its metabolites increases, which is expressed in an increase in DOPAC/DA in the hippocampus [52].

In the hypothalamus under chronic stress, there is a decrease in dopaminergic activity, as evidenced by a decrease in the HVA/DA and DOPAC/DA ratios [51]. The decrease in the ratios of 3-MT/DA and DOPAC/DA in the present study in the 2nd, 4th and 5th groups, as well as HVA/DA in the 4th and 5th groups, indicates that the after simulation of surgical interventions in the upper jaw, as well as in the area of the maxillary sinus provokes a high stress response, which goes into the phase of maladaptation.

5. Conclusions

After simulating sinus lifting with immediate implantation and dental implantation complicated by maxillary sinusotomy, there is an increase in the concentration of dopamine metabolites 3-MT, HVA and DOPAC, but at the same time a decrease in dopaminergic activity of the hippocampal formation, compared with simulation of septoplasty and simple damage to the alveolar ridge of the upper jaw. Most likely, such changes are explained by the disruption of the adaptive response in the early postoperative period in the absence of analgesic therapy and correction of stress reactions.

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Article

Advantages of bilateral cochlear implantation

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Abstract: The authors studied the indicators of speech intelligibility – a critical indicator of the effectiveness of cochlear implantation (CI) in patients with deafness. The purpose of the study was to compare results of speech audiometry in deaf patients with single-side and bilateral cochlear implantation (CI). The study was conducted in children aged 6 to 17 years with matured speech skills. The results showed that speech intelligibility in group with bilateral CI higher than in single-side CI group. Bilateral cochlear implantation has more potential for efficient speech rehabilitation than single-side CI.

Keywords: deafness, cochlear implantation, speech audiometry.

Citation: Pashkov A., Voevodina K., Naumova I., Popadyuk V., Pashkova A. Heart Rate Variability, Advantages Of Bilateral Cochlear Implantation Otorhinolaryn-gology, Head and Neck Pathology (ORLHNP). 2023; 2 (4): 28-30

https://doi.org/10.59315/ORLHNP.2023-2-4.28-30

Academic Editor: Valentin Popadyuk

Received: 13.12.2023
Revised: 20.12.2023
Accepted: 01.01.2024
Published: 30.01.2024

1. Introduction

Cochlear implantation (CI) is a technology of insertion an electrode system in the cochlea to stimulate the auditory nerve with subsequent rehabilitation. This is the method of choice for patients with bilateral deafness associated with damage to the cochlea. In recent years, according to various studies, there has been a steady increase in the number of children with bilateral sensorineural deafness who underwent CI on both sides [1]. The choice of this solution is mainly reasonable by the possibility of determining the sound source in space (ototopic) and the relatively higher rates of speech intelligibility, which become available due to spatial hearing in bilateral CI [2].

Traditionally bilateral hearing provides intelligibility, localization of the sound source, understanding of speech in a noisy environment and sound perception with sufficient volume. One of the functions of the auditory analyzer is to isolate "useful" sound/speech information, including from several sound sources, which "asymmetric" hearing cannot potentially provide [3]. In a complex acoustic space, a person's head creates a shadow effect, which works as an acoustic barrier and weakens the intensity of the sound signal, including speech on the one hand. The effect of noise reduction is the ability of the brain to isolate a useful auditory (speech) signal coming binaurally. The mutual amplification effect, also known as loudness summation, refers to the same perception on both sides due to balanced action potentials emanating from both auditory nerves to the brain stem. Localization (ototopy) is the ability to perceive the direction of the sound source, which helps in orientation [4]. All these effects should be taken into account in the rehabilitation of patients with deafness who underwent CI surgery.

The number of children born annually with bilateral deafness is approximately 1 in 1000 [5], and the number of CI operations performed in the Russian Federation is in the range of 1500 annually, which imposes additional requirements on the constant search for solutions to improve the effectiveness of cochlear implantation.

2. Patients and Methods

The present study analyzed the data of 61 patients with bilateral sensorineural deafness (n=61) who were users of the CI system. The age of the subjects varied from 6 to 17 years (Me=12±2.9). By gender, patients were distributed as follows: girls - 37.7% (n=23), boys - 62.3% (n = 38). Unilateral cochlear implantation was performed in 54.1% of cases (n=33), bilaterally in (n=28) 45.9%. The default sound processor (SP) microphone gain was 90% in all observations. Criteria for non-inclusion in the study were: abnormal development of the cochlea, previous meningococcal infection, incomplete insertion of the electrode array into the cochlea, or deactivation of one or more electrodes. To assess speech intelligibility, all children underwent speech audiometry via processor in a free field. The study was carried out according to the traditional method: with the supply of speech material with an intensity of 65 decibels (dB) of sound pressure level (SPL) through loudspeakers located at an angle of 45° at a distance of 1 meter from the SP microphone. Speech audiometry was performed in a quiet environment. The residual noise level was less than 50 dB SPL.

Statistical analysis

Statistical analysis was performed using the IBM program © SPSS Statistics New Seas Subscription © version 25.0.0. The sample was tested for normal distribution using the Smirnov-Kolmogorov and Shapiro-Wilk tests (p-value≥0.05).

Descriptive statistics were used with the calculation of the mean, standard deviation, median, mode, standard error of the mean, analysis of frequency tables. An exploratory analysis was used to compare speech intelligibility scores in patients with unilateral and bilateral cochlear implantation.

3. Results and discussion

All patients demonstrated a high level of development of auditory speech skills: speech intelligibility ranged from 33 to 100% (Me=90±14.2) In the group of patients with unilateral CI, speech intelligibility ranged from 33% to 100% (Me=87.0±17); in patients with bilateral implantation, speech intelligibility ranged from 78 to 100% (Me=93.5±5.8). Analysis of the data showed that the group of patients with bilateral cochlear implants demonstrated higher speech intelligibility scores compared to patients who underwent CI on one side (Fig. 1.) A statistically significant relationship was established between the number of cochlear implants in a patient and speech intelligibility scores (p =0.046).

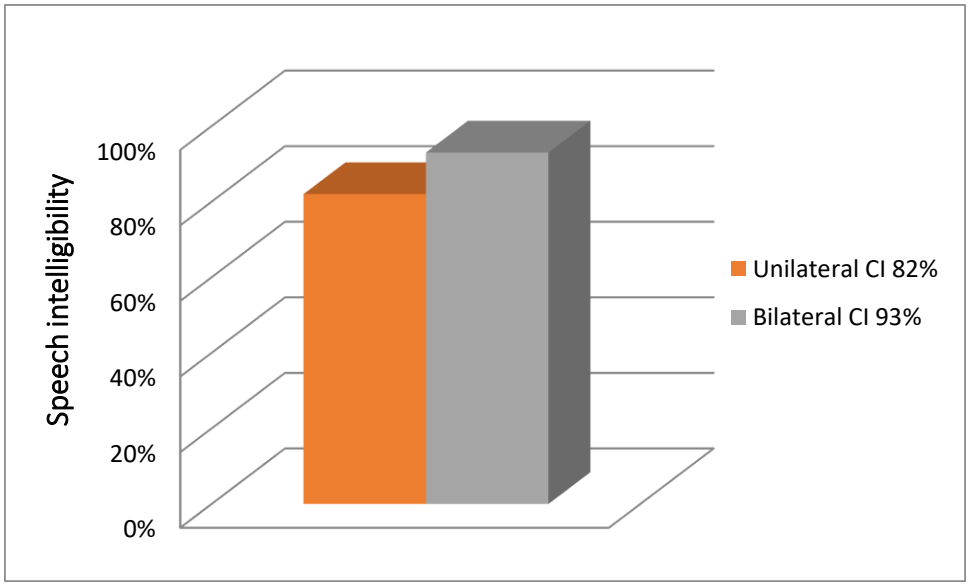

Figure 1. Speech intelligibility in patients with unilateral and bilateral CI.

4. Conclusions

The data obtained show that children with bilaterally installed CI systems have higher rates of speech intelligibility, which potentially brings them closer to their normal hearing peers in terms of cognitive development. However, bilateral cochlear implantation alone does not allow patients to achieve the same level of academic achievement as their normal hearing peers, even taking into account the duration of deafness and the timing of the surgery [6]. There are other factors that explain the differences in academic performance between children with bilateral CI and normal-hearing peers. These reasons include the possible lack of coordinated activation of the microphones of the processors of both ears to the incoming stream of speech information, as well as the discrepancy in the presentation of the contacts of the electrode array and the tonotopic representation of one or another frequency region of the organ of Corti [1]. If the solution of the first problem has a purely technical basis and can be performed during the evolution of CI systems, then the discrepancy in the anatomical parameters of the depth of insertion of the CI electrode array and the location in the cochlea requires further study using radiation diagnostic technologies.

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

Funding: Not specified.

Institutional Review Board Statement: Informed consent was obtained from all subjects involved in the study.

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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Heart Rate Variability, Pain Syndrome and Cortisol Concentration in Oral Fluid During Sinus-Lifting And Dental Implantation

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Abstract: Acute pain serves as an important biological function because it warns of the degree of damage or its potential deterioration. This is a rapid response to a harmful stimulus that does not lead to long-term consequences [1]. On the other hand, it can have various psychological and emotional consequences. Attention is therefore focused on aggressive prevention and treatment of acute pain to reduce complications and progression of chronic pain conditions.
The study of pain syndrome after dental surgery is still relevant [2, 3], since in clinical [2-11] and experimental studies [12-20] it was shown that surgical interventions in the maxillofacial region entail a cascade of stress reactions [21, 22].

Keywords: sinus-lifting, dental implantation, acute pain, chronic pain, surgical interventions.

Citation: Dragunova S., Samoilova M., Ganshin I., Chernolev A. Heart Rate Variability, Pain Syndrome and Cortisol Concentration in Oral Fluid During Sinus-Lifting And Dental Implantation Otorhinolaryngology, Head and Neck Pathology (ORLHNP). 2023; 2 (4): 31-36

https://doi.org/10.59315/ORLHNP.2023-2-4.31-36

Academic Editor: Valentin Popadyuk

Received: 13.12.2023
Revised: 20.12.2023
Accepted: 01.01.2024
Published: 30.01.2024

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

1. Introduction

Acute pain serves as an important biological function because it warns of the degree of damage or its potential deterioration. This is a rapid response to a harmful stimulus that does not lead to long-term consequences [1]. On the other hand, it can have various psychological and emotional consequences. Attention is therefore focused on aggressive prevention and treatment of acute pain to reduce complications and progression of chronic pain conditions.

The study of pain syndrome after dental surgery is still relevant [2, 3], since in clinical [2-11] and experimental studies [12-20] it was shown that surgical interventions in the maxillofacial region entail a cascade of stress reactions [21, 22]

2. The purpose of the study.

To determine the most adequate anesthesiological aid regimens in patients with sinus-lifting with simultaneous dental implantation by minimizing stressors.

3. Materials and methods.

Before surgical manipulation, electrodes for ECG recording were applied to the patient, then oral fluid was taken by chewing special tampons by the patient for subsequent evaluation of cortisol therein.

Sinus-lifting was performed with simultaneous dental implantation. Deproteinized porcine spongiform bone, Ovis XENO-P xenogenic porcine bone material (DENTIS, Korea), was used as osteoplastic material. Titanium dental implants (Alpha Bio, Israel) were used as the implant.

After the end of the surgical manipulation, saliva was repeatedly taken by this method and the electrodes were removed.

Patients were randomly assigned to 3 groups who were orally prescribed non-steroidal anti-inflammatory drugs of various classes: eterocoxib, nimesulide, ketorol.

Three-time sampling of oral fluid was carried out. Patients were asked to chew a special swab for 3-4 minutes. A comparison group was formed, which was made up of 25 healthy men and women aged 20 to 37 years. Oral fluid sampling in the comparison group was carried out between 10:00 and 16:00. The taken material was subjected to electrochemiluminescent immunoassay

HRV was assessed based on an analysis of electrocardiogram records. ECG was carried out using the Varikard hardware and software complex. The following ECG intervals were evaluated: before the oral examination, 20±4 minutes; from the moment of anesthesia until the end until the start of surgery, 76±14 minutes; from the end of the surgery until the end of the second intake of oral fluid, 16±4,5 min..

A day later, patients were invited for re-examination to assess the implant, assess the intensity of pain syndrome and record an ECG.

4. Study results.

Pain syndrome. One hour and three hours after surgery, patients in Group 3 had the most severe pain syndrome compared to patients in the remaining groups ($p < 0.001$). After 6 hours, patients in Group 2 had significantly lower pain intensity than patients in Group 3 ($p < 0.05$), but higher pain intensity than patients in Group 1 ($p < 0.01$).

A day after the end of the operation, patients of Group 1 had practically no pain syndrome, and pain in patients of Group 2 was lower than in patients of Group 3 ($p < 0.001$). At this time, patients in Group 2 had significantly higher pain intensity than in Group 1 ($p < 0.01$). After 48 hours, patients in Groups 1 and 2 had no pain, and patients in Group 3 had mild pain, which was higher than in the first two groups ($p < 0.01$).

On the facial pain scale, severe pain syndrome was noted only in the third group during the first 3 hours.

Changes in heart rate variability. The dynamics of changes in the ultra-low-frequency component of the HRV. 20 minutes after the end of surgery, ULF significantly decreased in group 3 ($p < 0,001$) and remained the same over the next 24 hours. In the first group, ULF significantly increased compared to the moment of surgery ($p < 0.01$), and no changes occurred after 24 hours. In the second group, this indicator throughout did not have dynamics. At 120 minutes of ECG monitoring, ULF was significantly lower in patients in Group 3 compared to patients in Groups 1 and 2 with no differences at that time point. A day later, ULF was significantly lower in Group 2 than in Group 1 and higher in Group 3 ($p < 0.01$) and lower in Group 3 than in Group 1 ($p < 0,001$).

The dynamics of changes in the very low-frequency component of the HRV. VLF was higher in Group 1 patients compared to Group 2 and Group 3 ($p < 0,001$) patients. Patients in Group 3 had significantly lower very low-frequency component values at the specified time point than patients in Group 2 ($p < 0.05$). Every day after surgery, the values in Group 2 were significantly higher than in Group 3 ($p < 0.001$), but lower than in Group 1 ($p < 0.01$).

The dynamics of changes in the low-frequency component of the HRV. The low-frequency component values had fewer differences than the above-described HRV values. So, before, on time and immediately after the closed sinus-lifting with simultaneous implantation, there were no statistically significant differences either between the estimated periods or between the groups. But it should be noted that after the end of surgical manipulations in the second group, LF was significantly lower than in the 1- group ($p < 0.05$), and higher than in the 3rd group ($p < 0.01$). A day after the operation, LF in all groups increased significantly ($p < 0.01$), but in the 3rd group it was significantly lower, we in the remaining groups ($p < 0.001$).

Dynamics of changes in the vagosympathic index. An inter-group comparison showed that no differences were identified before and during surgery. After surgery, Group 2 had a significantly lower LF/HF ratio than Group 1 ($p < 0.01$) and a significantly lower LF/HF ratio than Group 3 ($p < 0,001$) than Group 1 ($p < 0,001$).

Changes in cortisol concentration in oral fluid. Compared to a group of healthy individuals, patients in all three groups before surgery had no significant difference in cortisol concentration. At 20 minutes after surgery, cortisol was significantly higher in Group 1 than in the comparison group ($p < 0.01$). Patients who took nimesulide and ketorol also had higher cortisol values than healthy individuals ($p < 0.001$). The comparison group and patients from the etericoxib group did not differ significantly in the day after surgery, but its concentration was significantly higher in the 2nd ($p < 0.05$) and 3rd groups ($p < 0.001$). Cortisol concentration was significantly higher in Group 2 after 20 minutes of surgery than in Group 1, but lower in Group 3 ($p < 0.01$). In the etericoxib group, its concentration was significantly lower than in the ketorol group ($p < 0.001$). A day after the end of closed sinus-lifting with single-stage implantation, the highest cortisol level was recorded in patients of group 3, compared with patients of other groups ($p < 0.001$). At the same time, the 1st and 2nd groups did not differ significantly from each other.

5. Discussion.

The choice of analgesics is based on previous safety and tolerability studies. Nonsteroidal anti-inflammatory drugs (NSAIDs) cyclooxygenase-2 (COX-2), which selectively blocked the isoenzyme TsOG-2, were designed to limit the side effects of NSAIDs. Etoricoxib is known to be a selective inhibitor of the TsOG-2 enzyme. It is an effective analgesic that is associated with a reduced risk of bleeding due to platelet dysfunction, gastrointestinal bleeding, and ulcers [23, 24]. No gastrointestinal adverse events were noted in the present study.

Etoricoxib had significant anti-inflammatory efficacy and had beneficial effects on local postoperative trauma than tramadol. The reduction in inflammation caused by etoricoxib and tramadol on day 5 was significantly higher (86.67% and 70%, respectively). On the other hand, only about 13% of patients treated with etoricoxib reported mild inflammation even on Day 5, while 30% of patients treated with tramadol reported mild inflammation on Day 5.

A higher percentage of patients taking etoricoxib (30%) reported both pain reduction and unrestricted mouth opening. compared to those taking tramadol (23%). The results of the unpaired t-test revealed a difference in the efficacy of etoricoxib compared to tramadol. The difference was extremely significant on days 2 and 4, while a significant difference existed on all other days.

There was a long-lasting analgesic effect when treated with etoricoxib. Patient assessment results showed a statistically significant difference in pain reduction for etoricoxib (93.34%

reported no pain) compared to tramadol (60% did not experience pain) at the end of 5 days. In the present study, it was the ethericoxib group that showed the smallest pain syndrome compared to the nimesulide and ketorol group.

The data obtained in the present study are supported by data from other authors. Thus, patients taking LVTD from the group of non-selective COX inhibitors had more pronounced sympathicotension, greater tension of the autonomic nervous system, as a result of their smallest analgesic activity, and more pronounced effects on other organs and systems [25], compared to selective TsOG-2 blockers.

6. Conclusions.

As a result of the analysis of the intensity of postoperative pain syndrome, the assessment of heart rate variability and cortisol concentration in the oral fluid, it has been found that the use of selective blockers TsOG-2 from the coxibes group compared to non-selective cyclooxygenase blockers and blockers is predominantly TsOG-2, reduces intensity of stress reactions, leads to less secretion of cortisol by salivary glands during a day and improves postoperative course of patients during the first three days undergoing sinus-lifting with simultaneous dental implantation.

The use of non-steroidal anti-inflammatory drugs during sinus-lifting with simultaneous dental implantation in patients in the perioperative period from the class of non-selective TsOG-2 blockers and from the class of predominant TsOG-2 blockers leads to greater secretion of cortisol by the salivary glands during the day (20 minutes after surgery - 23,67±1,29 nmol/L and 27,43±1,34 nmol/L, respectively) after surgery, compared to selective TsOG-2 blockers (18,04±1,73 nmol/L).

Diagnosis of pain syndrome after sinus-lifting with simultaneous dental implantation using a digital rating scale and a facial pain scale can be accurate only with pronounced pain intensity (above 31,09±2,82 mm by CRS).

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

Acknowledgments. Scientific article.

Author Contributions: Conceptualization, S.G., M.V.and I.B. A.I.; methodology, S.G., M.V. and A.I.; software, S.G.; validation, M.V., A.I., I.B. and S.G.; formal analysis, A.I.; investigation, M.V. and S.G.; resources, X.X.; data curation, K.L..; writing—original draft preparation, K.I. and G.M.; writing—review and editing, M.V., I.B. and S.G.; visualization, A.I.; supervision, S.G.; project administration, S.G. 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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Case series

Transient Macular Edema after Uncomplicated Cataract Surgery: Below the Surface

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Citation: Beisekeeva J., Samoylenko A., Kochergin S.Transient macular edema after uncomplicated cataract surgery: below the surface. Otorhinolaryngology, Head and Neck Pathology (ORLHNP). 2023; 2 (4): 37-47. https://doi.org/10.59315/ORLHNP.2023-2-4.37-47

Academic Editor: Valentin Popadyuk

Received: 13.12.2023
Revised: 20.12.2023
Accepted: 01.01.2024
Published: 30.01.2024

Abstract

Purpose: To present analysis of 17 case reports of 17 patients who had an acute transient macular edema appeared after uneventful cataract surgery.

Observations: In literature about 12 case series of toxic macular edema development after cataract surgery are described and all of them were accompanied by the cefuroxime intracameral usage. Also, there are reports of macular edema development after several weeks after uncomplicated phacoemulsification due to pseudophakic cystoid macular edema (Irvine-Gass syndrome) or due to vitreomacular traction syndrome. We observed a series of transient acute macular edema with 3,8% incidence occurring on the first days after uncomplicated phacoemulsification with IOL implantation that had no signs of vitreomacular traction or acute inflammation. Optical coherence tomography (OCT) was performed on patients complaining on blur vision and who had signs of macular edema by ophthalmoscopy. By OCT high and often extensive neuroepithelium and local pigment epithelium detachments were observed on the first day after surgery in 17 patients with quiet postoperative condition of the eye. The edema resolved on the 3-6-th day by standard phaco accompanying pharmacological treatment. In most cases posterior vitreous cortex was adjacent to the retina except 3 patients with posterior vitreous detachment in macular area. We found a paper by Costen M.T.J. et al. (2007) about the same striking appearance of maculopathy called by authors "A-sign" maculopathy because of A-shaped pattern on OCT images in 3 patients after routine cataract surgery. Yaman A (2008) and Panagiotidis D (2010) also reported same findings after uncomplicated cataract surgery. We compared our findings with 3 papers mentioned above, as well as with typical pseudophakic cystoid macular edema (CME) and vitreomacular traction syndrome.

Conclusion: It's obvious that observed case series are cefuroxime induced. But its comparison with CME in terms of morphology of the macula could improve our understanding of mechanisms of the interstitial fluid flow in the eye tissues.

Keywords: macula; pseudophakic cystoid macular edema; phacoemulsification; Irvine-Gass syndrome.

1.Introduction

In 2014-2015 we observed unusual cases of transient macular oedema in 17 patients after a routine cataract surgery with peri-operative topical usage of non-steroid, steroid anti-inflammatory drugs and antibiotics including standard dose of intracameral cefuroxime (1 mg/0,1 mL). An anterior segment of the eye was clear and calm but patients complain on blur vision. On the OCT there were neuroepithelium detachment with local pigment epithelium detachment that resolved in 3-6 days on standard anti-inflammatory treatment. Patients stayed in the hospital until full recovery. We had not found similar cases at that time [1]. But recently we have discovered in the «Nature» similar cases described by Costen M.T.J. with colleagues in 2007 for the first time, and this paper suggests us the necessity of publication of our cases.

2. Material and methods:

literature overview, retrospective analysis of medical documentations of 17 cases including the age, sex, presence of associating diseases and drug treatment, length of the eye, keratometry, intraocular pressure (IOP) and OCT image of the macular region made by RTVue-100 (Optovue®, USA).

3. Results

The average age of patients was 68,24 ± 9,71 years old (50-82). The men women ratio was 14:3. The phacoemulsification with IOL implantation (Acrysof IQ, Alcon®, USA) was performed under a combination of topical and subtenon anesthesia through a 2,4 mm incision. A cataract density mostly was about 2-3 degree but patient №13 was with soft posterior subcapsular cataract and patient №3 with mature hard 4-degree cataract. All operations were carried out by the same trained surgeon on the «Millenium» machine (Baush&Lomb®, USA) by the "cross" method on the Burst mode with a maximum ultrasound power of 40%, vacuum 250 mm Hg and with the velocity of passive irrigation of balanced salt solution about 90 sm^3/min. All IOLs were implanted in the capsule bag. During the period from the beginning of 2014 until the end of 2015 there were 449 phacoemulsifications performed by the mentioned surgeon. Thus, the incidence of occurred acute transient macular edema (ATMO) was 3,8%.

Three patients had bilateral compensated primary open angle glaucoma at the different stages (patients № 2, 12 and 15), and one of them underwent the trabeculectomy a year ago (№15). There were three patients with a mild and high myopia (№ 1, 7 and 14).

The most common associated disease was systemic arterial hypertension – 15 from 17 cases. Also, the permanent form of atrial fibrillation was mentioned (patients № 2 and 4). Implanted sinus pacemakers were observed in 3 patients (№ 2, 10 and 16). Patients № 10 and 16 suffered from the coronary heart disease and underwent vessel's stenting. Beside the cardiovascular diseases there were a nephrolithiasis and hydronephrosis (cases № 10,14, 17), a cirrhosis of the liver (case № 7) and a rheumatoid arthritis (cases № 4 and 16).

Three patients suffered from the diabetes mellitus: two of them were insulin-dependent (patients № 6 and 7) and one (patient №11) took hypoglycemic drugs orally. None of them had sighs of diabetic retinopathy. Among constantly taking antihypertensive medications there were a diuretic (patients № 1,11) and ß-blockers (patients № 8,11 and 12). Antiplatelet drugs ("Cardiomagnil") was taken by two patients (№8 and №16).

Patient №3 with mature cataract was in the interval between chemotherapy courses for breast cancer with metastases.

The second eye was pseudophakic in 5 patients.

The mean uncorrected visual acuity before surgery was 0,11±0,11, and corrected 0,21±0,18. In spite of presence of macular edema the mean corrected visual acuity on the first day after surgery was 0,31±0,20. When the macular edema resolved the mean uncorrected visual acuity was 0,48±0,28 and the best corrected visual acuity was 0,82±0,16.

IOP before surgery was 21,18±2,38 mm Hg. On the first days after the surgery the IOP was within the normal values and was 19,5±3,2 mm Hg at patients' discharge.

The mean length of the eye was 23,93±1,23 mm (22,45-26,2 mm), the mean keratometry along two main meridians was 43,41±1,41 D (40,1- 45,5 D).

Postoperative inflammatory reaction was minimal: one male patient (№1) had +1 cell reaction in the anterior chamber's aqueous humor on the first day after surgery. All patients receive medical treatment: instillations of non-steroidal anti-inflammatory drugs (Indocollyre 0,1%), dexamethasone 0,1% and ciprofloxacin 0,4% 4 times a day, and subconjunctival injections of the dexamethasone 0,3 ml 0,4% № 2-5.

A high detachment of the neuroepithelium in the macular region was observed on OCT in the majority of cases on the first day after surgery due to liquid accumulation in the outer nuclear layer and under the photoreceptors layer. Local pigment epithelium detachment also was detected. This typical swelling resolved in 3-6 days. The OCT image of patient №9 on the first day after surgery with high (772 mkm) detachment of the neuroepithelium is presented on Figure 1. On the third day after surgery the detachment of the neuroepithelium has almost resorbed, with only a tiny detachment of the photoreceptor's layer left which disappeared on the fourth day.

Changes that were observed on the OCT between the second and fifth day in case №3 are represented on the Figure 2.

"A-pattern" of the retinoschisis described by Costen M.T.J. et al. was mentioned only in case №5 which also had a posterior vitreous detachment (PVD) (Figure 3).

There is an interstitial swelling of the outer retina layers resulting in partial or total neuroepithelium detachment in the majority of cases. On the OCT images in the fovea region above the detached bodies of the photoreceptors there are low-differentiated shapeless structures that in some cases had radial direction and could represent Henle fibers or swelled Muller cells' bodies and processes locating in the radial direction on the frontal plane [2].

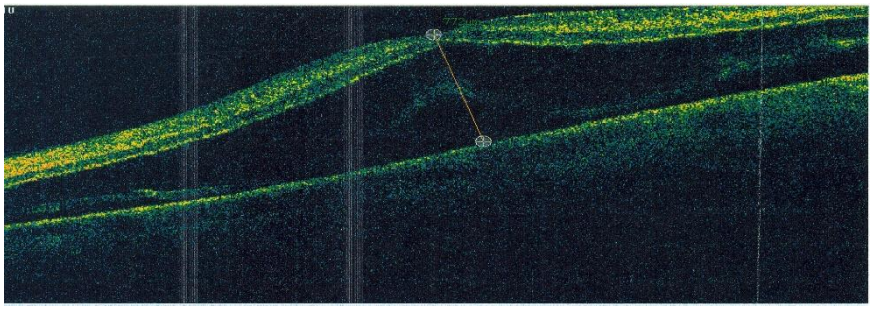

Figure 1. OCT image OD of case 9 on the 1st day after surgery. 772 mkm neuroepithelium detachment

Patient №6 had hard drusen and dyspigmentation in the macula region observed ophthalmoscopically but on the OCT there are only pigment movement in the complex pigment epithelium – Bruch's membrane – chorocapillaries (Figure 4). Interesting to note that none of the patients had structures with high optical density such as large drusen or neovascular membranes.

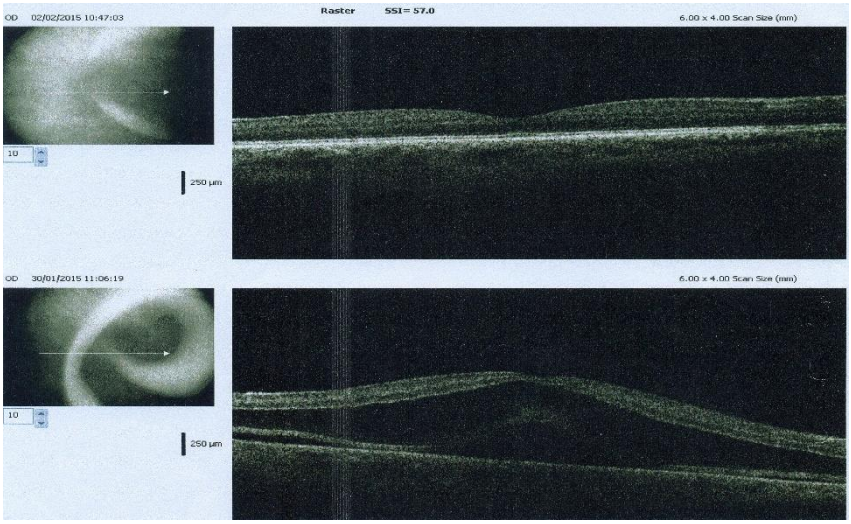

Figure 2. OCT OD of case 3 on the 2nd (below) – 5th (top) days

OCT images of the patients №7 and №14 are similar to those that are observed in pseudophakic cystoid macular edema with cysts in the outer plexiform and nuclear layers (Irvine-Gass syndrome) (Figure 5 and 7).

The lowest detachment of the neuroepithelim on the first day was observed in patient №8 (Figure 6). Nevertheless, the enlargement of the outer nuclear layer, appearance of optical voids in the outer plexiform layers and detachment of the photoreceptors with or without the pigment epithelium in some cases local and in some cases throughout the whole macula region.

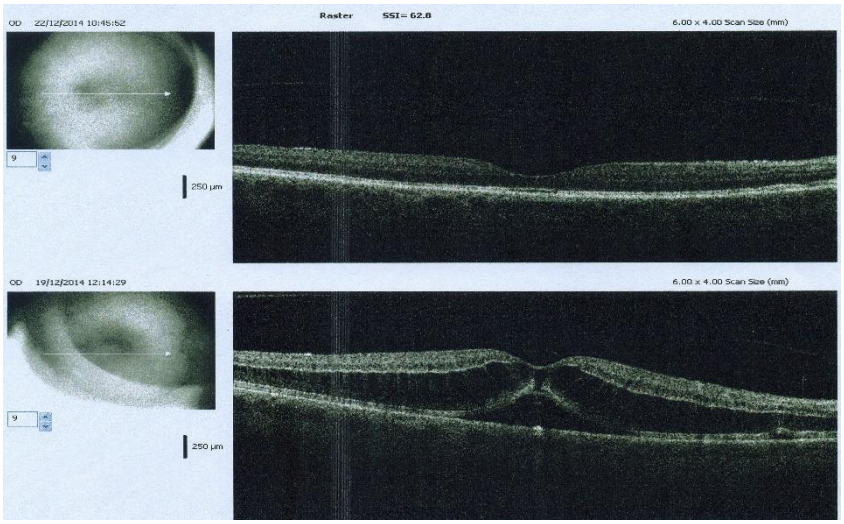

Figure 3. Dynamic on OCT OD of case 5: 3d day (below) and 6th day (top), «A-sign», PVD

The OCT image of the patient №14 with a high myopia on the second day after surgery is represented on the Figure 7. Worthy to note the small size of the cysts in the outer nuclear layer. Complete resorption of edema was observed on the third day after surgery.

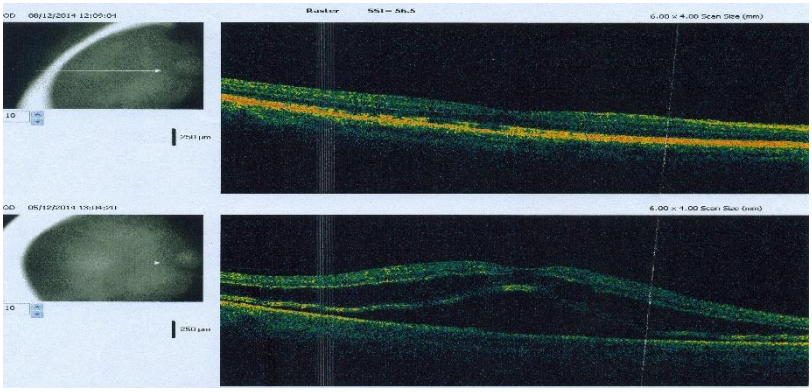

Figure 4. OCT OD dynamics of case 6 on the 2nd (below) - 5th (top) days

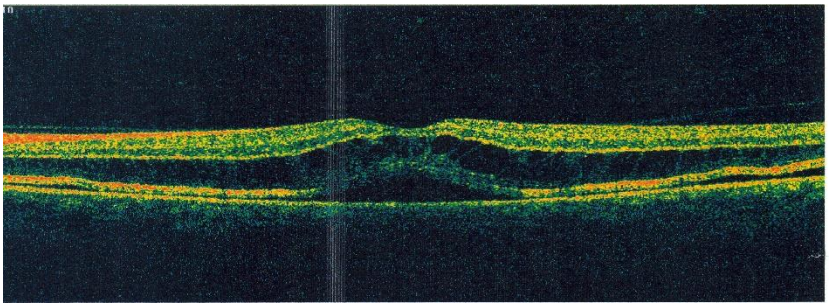

Figure 5. OCT OS dynamics of case 7 on the 3d day, no PVD

In patient №15 with surgically treated stage III and IOP normalized glaucoma the resolution of the edema was detected on the sixth day (Figure 8).

On the OCT images of the patient № 16 (Figure 9) and patient № 17 (Figure 10) beside the neuroepithelium detachment the epiretinal fibrosis was detected which has not changed after resorption of the edema. Patient № 17 had complete resolution on the 4 – 5th day.

There was no PVD in the macula region in 9 cases. Sometimes the posterior hyaloid was elevated on the sides of the detached neuroepithelium but lay down again after the resorption of the oedema. In spite of high neuroepithelium detachment the foveal pit remained in all cases which means that the structure of the inner retina layers that normally may suffer from a vitreous traction was saved during observed condition.

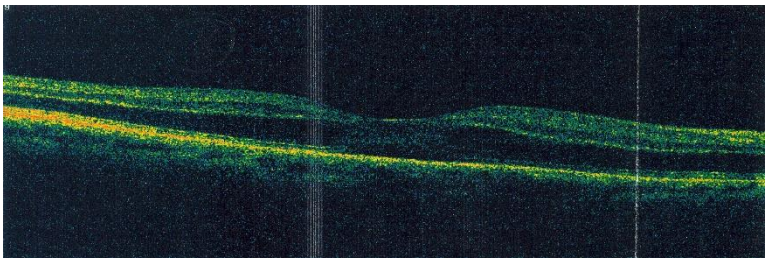

Figure 6. OCT image OS of case 8 on the 1st day

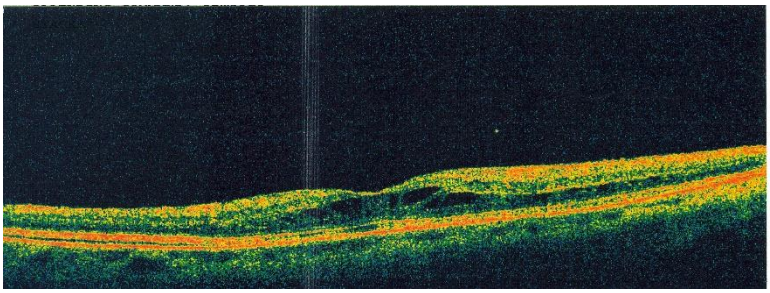

Figure 7. OCT image OD of case 14 with high myopia on the 2nd day

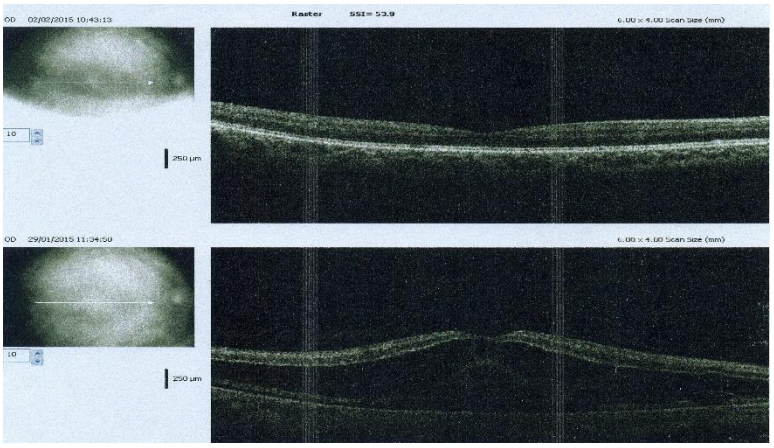

Figure 8. OCT OD dynamics of case 15 on the 2d (below) - 6th (top) days, POAG

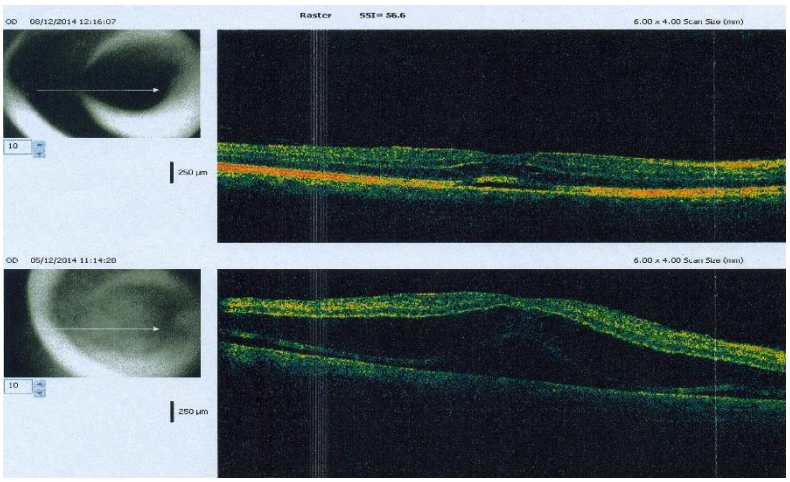

Figure 9. OCT OD dynamics of case 16 on the 2nd (below) and 5th (top) days, ERM

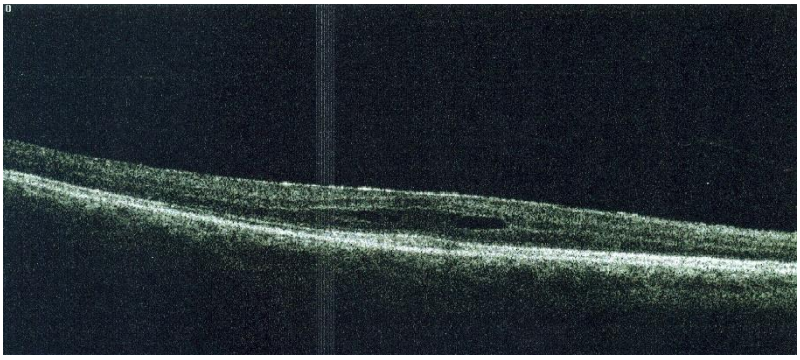

Figure 10. OCT image OD of case 17 on the 2nd day, SRD and ERM

Thus, on the majority of the images there are cavities in the outer nuclear layer which merge and split inner and outer nuclear layers. Also, there is detachment of the photoreceptors and the pigment epithelium but the order of this processes is unknown. Complete anatomical recovery of the macular region on the OCT usually occurs on the fourth day (3-6 days) after the surgery. Associated glaucoma, diabetes mellitus, treatment with diuretics influenced little on the area and height of the edema.

4. Discussion

Costen MTJ et al. in 2007 described similar cases. The incidence of them was not mentioned. Patients were two women and a man at age 72, 59 and 66 years old respectively. In the paper authors mentioned that all three patients had no signs of PVD but on the OCT image of the second patient there is almost a total PVD indicated except the foveal region where a contact with the internal limiting membrane is observed (http://nature.com/articles/6702587). British colleagues confused to determine the cause of the oedema but supposed that vitreomacular traction could be the reason of the described cases [1].

"A-sign" OCT image pattern described by Costen MTJ et al. may be explained by the structure of Muller cells that form a carcass in the macula region. The horizontal bar of the A sign probably is the part of this carcass as a part of the outer limiting membrane. A side bars sometimes wavy, sometimes compact and straight, which were noted on the OCT images, go up from the detached photoreceptors in the fovea, form an inverted trapezoid, and highly likely represent Henle fibers layer [2-4], which is located in tight connection with the Muller cells in the parafovea region. Matet A et al. in 2015 by the immunohistochemistry and the OCT detected a Z-like location of the Muller cells' processes in the sagittal plane: oblique path in the outer plexiform layer together with Henle fibers and vertical path in the inner retinal layers forming bonds with axons of the cones [5].

In 2008 Aylin Yaman et al perform a prospective study with 59 patients (59 eyes) who underwent cataract surgery. Macular swelling on the first day after the surgery was detected in 2 patients (3,3%) and its resorption has been occurred during a week. Patients had a total PVD after resorption and no sign of leakage on the fluorescent angiography. Authors considered that the cause of the described two cases was a vitreo-macular traction [6].

In 2010 Panagiotidis D et al. retrospectively described five cases of the acute macular swelling on the first day after the routine cataract surgery which are also resolved spontaneously in ten days due to PVD as authors supposed [7]. Traction genesis of the swelling also was suggested,

but the authors noted the common pathogenesis with a pseudophakic cystoid macular edema. "A-sign" pattern was mentioned in 2 cases. The incidence of those cases was 1:600 but authors mentioned that it should be higher in fact. One patient with a structural change in the pigment epithelium complained on metamorphopsia even after edema resorption as well as the two patients described by Costen MTJ et al.

Idiopathic traction macular syndrome which was described in 1967 by Jaffe NS [8] and in 1970 by Reese AB [9] is characterized by a partial detachment of the posterior hyaloid in case of its tight adhesion to the inner limiting membrane and results in changed foveal contour. This condition may spontaneously resolve in 10% of cases without a macular hole formation but only on condition of complete PVD [10-12]. There are rare cases of the macular holes occurring on the first day after uncomplicated cataract surgery in the literature [13,14]. Also, there are conditions documented when after a routine cataract surgery vitreo-macular adhesion and traction resulted in CME development refractive to anti-inflammatory drug treatment and resolved only after the vitrectomy [15,16].

The involvement of the vitreomacular adhesion in the pathogenesis of the observed cases is doubtful considering the intact foveal pit amid the high neuroepithelium detachment and the absence of the PVD after the resorption in most cases. The volume of the extracted lens is several times lower of the IOL, so there should be changes in the structure of the vitreous body under the action of anterior-posterior forces which could be involved in the pathogenesis of the macular holes [14]. But only in 3,8% of our cases and 3,3% of Yaman A. cases transient changes of the macular region were observed. Moreover, several prospective researches measuring by the OCT thickness of the macular region before and after the phacoemulsification, have found only minimal enlargement in the macula in early and late terms after surgery [17-19] and in 3,2% of cases CME [19].

We noted that the OCT images at the certain stages are similar to that in cystoid macular edema with still unknown etiology. But Irvine-Gass syndrome occurs on the 4-6 week after the cataract surgery. It is characterized by the leakage of the dye on the fundus angiography through the parafoveal capillaries at the late stages of the investigation and by the cysts in the outer plexiform and nuclear layers on the OCT. The risk factors of its appearance are: age, male gender, uveitis, diabetes mellitus, duration of the surgery, rupture of the anterior hyaloid, loss of the vitreous body [20,21]. In the era of small incision surgery, the incidence of this condition decreased and is about 1,17%. The additional risk factors are: epiretinal fibrosis, history of vitreoretinal surgery and branch retinal thrombosis. It was noted that high myopia, dry age related maculodystrophy and the usage of the prostaglandin analogues do not increase the incidence of the pseudophakic cystoid macular edema [22].

Gulkilik G. et al found that CME after uneventful phacoemulsification with IOL implantation is observed on the tenth week more frequently if there were signs of postoperative inflammation on the first days after the surgery as cell reaction 2+ in the aqueous humor - 43,2% versus 11,5% in case of absence of the cell reaction. The presence of the total PVD had a protective effect against CME development [23]. Many authors consider that the real incidence of the CME after routine cataract surgery is not 0,1 – 2,5% [24,25], but 10 times higher and may reach 25,5% which is confirmed by the investigations with the usage of fundus angiography [23,26]. Mentes J. et al detected that the incidence of CME found on the angiography after the phacoemulsification

is about 9,1% that is comparable with its incidence after the extracapsular methods of the cataract extraction [27].

Unlike our cases in CME there is a cystoid pattern on the OCT images and subretinal fluid with the detachment of the neurosensory retina is rarely observed [25].

Systemic cardiovascular and autoimmune diseases undoubtedly affect the level of microcirculation in all structures of the eye. A fluctuation of the IOP during the operation and release of inflammatory mediators due to tissue injury leads to changed permeability of the capillaries. There are cases of occlusion of the retinal microcirculation in the parafoveal region on the first day after cataract surgery in case of so-called paracentral middle maculopathy which is characterized by permanent paracentral visual field defects and ischemic hyper reflexivity in the projection of the deep capillary layer of the retina on the OCT images [28].

Ioshin I.E. considers that pseudophakic CME is developed when the velocity of the capillary filtration exceeds the outflow rate of the interstitial fluid from the retina through the perivascular pathways despite the auto regulation mechanisms, and probably some autoimmune reactions to the IOL play a role in this process [29].

The intracameral usage of cefuroxime is considered to be the cause of such conditions as we observed with serous retinal and pigment epithelium detachment [30,31]. The toxic effect of cefuroxime is thought to be the reason of structural changes of the macular region. Although the underlying mechanism of such individual reaction is unknown. But the goal of this paper is to pay attention to the similarity of the OCT images of ATMO and CME at the certain stages of the process. Avascularity of the foveal region makes it susceptible to any changes in the molecular or chemical compound of the intraocular and interstitial fluids. The fact that pseudophakic CME usually occurs 4 weeks after surgery and has an OCT image that resembles the resorption stage in ATMO suggests a late breakdown of some compensatory mechanisms normally providing the homeostasis in this region.

The resorption of the intra- and subretinal fluid took place simultaneously in the outer retinal layers and along an entire zone under detached photoreceptors mainly due to the reactivation of the retinal pigment epithelium ion channels and pumps. All patients had a native vitreous body. Structure features of the vitreous body described by Worst J. (1975), i.e., connection between the retrolental bursa and premacular bursa through the central channel, probably has an impact to the pathogenesis of the ATMO, and even subconjunctival injection of cefuroxime also causes macular edema [32].

5. Conclusions

Thus, the incidence of macular edema induced by the standard dose of cefuroxime is from 0,35% [30] to 3,8%. Men are more likely to develop this condition rather than women. These two features together with fluid accumulation in the outer nuclear layer are similar to CME and central serous chorioretinopathy but in contrast, there is no dye leakage on the fundus angiography [6,7,31]. The individual intolerance of the standard dose of cefuroxime revealed us a part of the mechanisms of resorption of the interstitial fluid that normally occurs in the posterior segment of the eye. It is known that one of the functions of the retinal pigment epithelium is ion-dependent water transport due to transepithelial potential difference [33]. Muller cells also play a huge role in the maintaining of water-metabolic balance of the retina. A new point of view on the development of macular diseases arose from the analysis of these case series [34].

The disadvantages of this study: it is retrospective, so OCT images were available only in the paper format. OCT scans were performed in linear regimes not in 3D which reduces the morphology details and its connection to the optic disc.

We hope that this study may help investigators to understand the mechanisms underlying the interstitial fluid circulation in the posterior segment of the eye and in the retina particularly. Further research is needed to reveal the fluid-tissue exchange in the retina.

Declarations:

Ethics approval and consent to participate

Not applicable.

Consent for publication

We obtained written consent from patients to publish this report.

Availability of data and materials

All data and materials in this article are available.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding or sponsorship was received for this study or publication of this article.

Artificial intellect usage: No AI was used to perform this article.

Authors' contributions

JB was a major contributor to the drafting of the manuscript and acquired all the data. AIS and SAK reviewed and edited the manuscript. All named authors take responsibility for the integrity of the manuscript as a whole and gave their approval for publication.

Acknowledgements: Not applicable

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Article

Stapedoplasty as a Method of Hearing Loss Treatment in Patients with Tympanosclerosis

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Abstract: Objectives: The aim of this study is to evaluate the efficacy of stapedoplasty as a method of hearing loss treatment in patients with stapes tympanosclerotic fixation.
Materials and Methods:The first group included 25 patients with CPOM and TSC who underwent a two-stage surgery (2nd stage – stapedoplasty). The second group included 25 patients with CPOM and TSC who underwent a one-, two-, or three-stage surgery with a typical sta-pedoplasty as a final step, but using a surgical CO2 laser.
Results: Analysis data of ABG mean values (35.3±8.6 dB before surgery) in TSC2 group showed their decrease in 1 month up to 22.1±9.5 dB; in 6 months – up to 17.0±8.0 dB, and in 12 months – up to 14.9±7.4 dB. Stapedoplasty with laser assistance was also effective, but its best results were shown in 6-12 months after surgery. ABG values ‹ 20 dB were reached in 76% pa-tients; from 20 to 30 dB – in 92%, and 30 dB – in 100% patients. Analysis data of BC values (30.3±11.3 dB before surgery) showed their consistency in 1 month after surgery – 31.1±13.2 dB; in 6 months – 28.9±13.1 dB, and in 12 months – 28.3 ± 12.8 dB.
Conclusion: Laser assistance during stapes crus crossing stage and stapedotomy in the early fol-low-up period results in absence of inner ear reaction for surgery.

Keywords: chronic purulent otitis media, tympanosclerosis, stapedoplasty, CO2 laser.

Citation: Kryukov A., Kunelskaya N., Garov Y., Zelenkova V., Zagorskaya E., Sudarev P. Stapedoplasty as a Method of Hearing Loss Treatment in Patients with Tympanosclerosis. Otorhinolaryn-gology, Head and Neck Pathology (ORLHNP). 2023; 2 (4): 48-56.

https://doi.org/10.59315/ORLHNP.2023-2-4.48-56

Academic Editor: Valentin Popadyuk

Received: 13.12.2023
Revised: 20.12.2023
Accepted: 01.01.2024
Published: 30.01.2024

1. Introduction

Surgical procedures in stapes with its tympanosclerotic fixation are not safe due to risk of sensoneural disorders developing. Another complication occurring due to this procedure is proth-esis refixation because of undertreated inflammation and lack of blood circulation [1,2,3,4,5,6].

Stapedoplasty in patients with chronic purulent otitis media (CPOM) is performed in 0.3% cases in the event of massive tympanosclerosis (TSC) and stapes tympanosclerotic fixa-tion with its mobilization inefficiency. Usually, stapedoplasty is carrying out in two steps: a tympanal mem-brane restoration (in 89% patients) and stapedoplasty proper [1,2,7,8].

Some authors recommend performing this method only in cases of severe bilateral con-duc-tive hearing loss in patients refusing of hearing aid [3]. The hazard of hearing loss and in-stability of stapes surgery results in patients with TSC are the main reasons of surgeons restrain relation to this method. The evidence of this problem are several articles elucidating 12-142 cases of different stapes procedures in patients with TSC; moreover, according to some data, stapedoplasty was per-formed only in 7-67 cases during last 20 years. Also, this problem is in-sufficiently illustrated in literature due to scarcity of stapedoplasty performing in TSC.

The aim of this study is to evaluate the efficacy of stapedoplasty as a method of hearing loss treatment in patients with stapes tympanosclerotic fixation.

2. Materials and Methods

Fifty patients with tympanosclerotic stapes fixation were examined and treated. In-formed consent for treatment and participation in clinical study was taken from every patient. Patients were divided into two groups depending on surgery technique. The first group (TSC1) included 25 patients with CPOM and TSC (10 males and 15 females, mean age 43.3±5.4 years) who underwent a two-stage surgery (1st stage – tympanoplasty, 2nd stage – stapedoplasty). All patients were conducted an instrumental stapedoplasty using different types of stapes prosthe-sis, mounted on the venous autograft, covering the vestibule window.

The second group (TSC2) included 25 patients with CPOM and TSC (9 males and 16 females, mean age 44.3±5.2 years) who underwent a one-, two-, or three-stage surgery with a typical stapedoplasty as a final step, but using a surgical CO2 laser.

Of 50 patients with TSC, in 41 CPOM cases a tympanoplasty type I (27 patients) and type III (14 patients) using automaterials – ear cartilage and temporal muscle fascia – (Woll-stein classification) were performed. Some patients underwent a one-stage surgery; in 9 cases of adhesive otitis media a stapedoplasty was performed [9]. As a second stage, 40 patients un-derwent a stapedoplasty after a successful tympanoplasty, and 1 patient underwent a cholestea-toma relapse removal (Table 1).

Table 1. Stapedoplasty types and stages in patients with TSC (n=50)

Groups	1st stage			2nd stage		3rd stage	Overall
	Tympanoplasty type I	Tympanoplasty type III	Stapedoplasty	Tympanum cavity revision	Stapedoplasty	Stapedoplasty	
TSC_1	18	7	-	-	25	-	50
TSC_2	9	7	9	1	15	1	42
Overall:	27	14	9	1	40	1	92

As a third stage, a stapedoplasty was performed in that patient with cholesteatoma re-lapse. As a method of hearing loss treatment in patients with TSC, 92 surgeries were per-formed, 50 of which were stapedoplasties (of these, 27 were vestibuloincudopexies, 19 – ves-tibulomyringopexies, and 4 were vestibulomaleolopexies). Types of prosthetic fastening were determined by the auditory chain elements mobility and integrity (Table 2).

Table 2. Stapedoplasty types and stages in patients with TSC (n=50)

Groups	1st stage		2nd stage			3rd stage	Overall
	vestibuloincudopexy	vestibulomyringopexy	vestibuloincudopexy	vestibulomaleolopexy	vestibulomyringopexy	vestibulomyringopexy	
TSC_1	-	-	18	4	3	-	25
TSC_2	3	6	6	-	9	1	25
Overall:	3	6	24	4	12	1	50

Indications for stapedoplasty performing were hearing loss, low-frequency ear noise, absence of drum membrane defects during a 1 year after reconstructive surgery, air-bone gap (ABG) › 30 dB in frequencies of conversational range, and TSC first surgery data. Surgery contraindications were elderly age (› 75 years) and patients' severe comorbidity.

In TSC1 group, as a first stage tympanoplasty type I was performed in 18 cases, and tympanoplasty type III was conducted in 7 cases. Stapedoplasty was performed in 12-22 months after tympanoplasty. After tympanic cavity intrameatal revision and autografts preparation, an instrumental stapedectomy was performed in 18 cases, and partial stapedectomy (a wide win-dow method) was performed in 7 cases. As a stapes prosthesis, we used patients' auricle carti-lage (length 3.5-5.5 mm) in 22 cases; in other 3 cases we used allocartilage, ceramics, and tef-lon. In all cases, stapes prosthesis was installed on a venous graft from foot dorsum, covering vestibule fenestra (Figure 1).

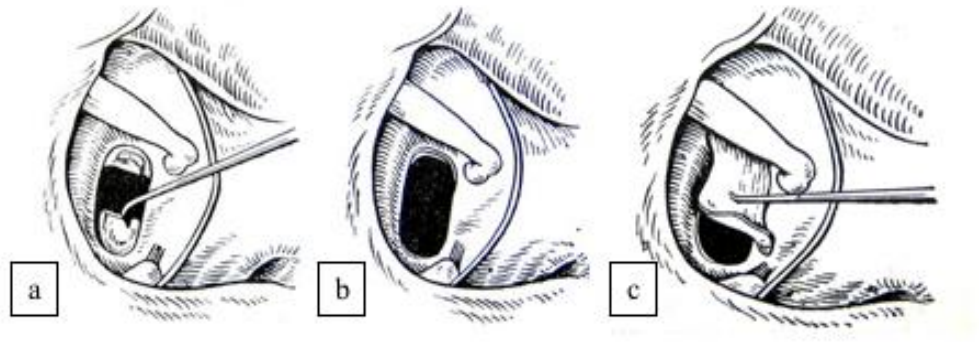

Figure 1. Stapedoplasty stages: a – footplate 2/3 removal (wide opened stapedotomy); b – footplate full removal (stapedectomy); c – oval window closing with autovenous graft.

Vestibuloincudopexy was performed in 18 patients with local sta-pes TSC; vestibulomaleolopexy was conducted in 4 patients, and vestibulomyringopexy was performed in 3 patients with diffuse TSC (Figure 2).

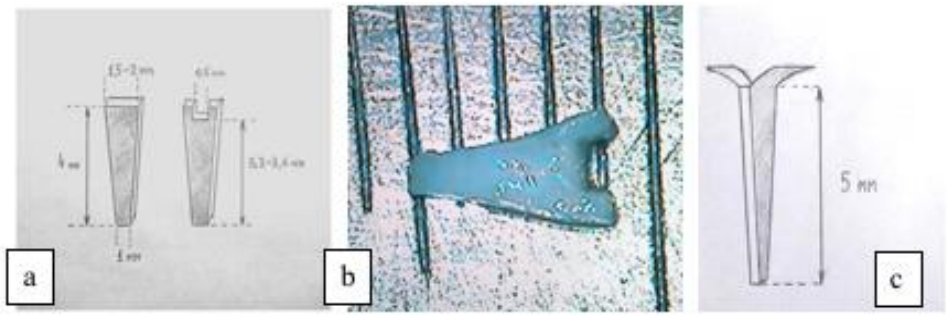

Figure 2. Types of autocartilage prosthesis application on the venous graft: a – vestibuloincudopexy with a joint-forming collar; b – vestibuloincudopexy; c – T-shaped vestibulomyringopexy.

In TSC2 group, as a first stage tympanoplasty type I was performed in 9 cases, and tym-panoplasty type III was conducted in 7 cases. In one case as a second stage a tympanic cavity revision was performed. As a final stage, in all 25 patients stapedoplasty with laser assistance technique was performed. Laser was used during stapedotomy and stapes crus crossing proce-dures. Stapedoplasty was the only surgery stage in 9 patients, the second surgery stage in 15 pa-tients, and the third stage surgery method in 1 case. Stapedoplasty was performed in 12-20 after tympanoplasty was conducted. Partial stapedotomy was performed in 14 cases; total stapedot-omy with autocartilage stapes prosthesis (prosthesis length 3.5-5.0 mm; for stapedotomy a su-perimpulse mode with flash scanner was performed; focus distance 250 mm, perforation diam-eter 0.7-1.0 mm, laser radiation power 16-24 W [mean value 21.9±2.1 W]) usage was per-formed in 11 cases. Partial stapedotomy was carried out by one impulse, whereas total stape-dectomy was carried out by several impulses. In case of necessity, posterior stapes pole was removed instrumentally (Figure 3).

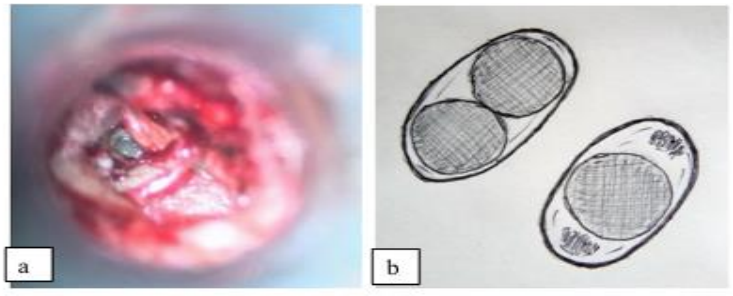

Figure 3. Footplate hole laser formation: a – micropicture of footplate formed hole (1 mm diam.); b –hole laser formation scheme.

A one-impulse hole in footplate was generated in 7 cases; in 18 cases due to thick and dense footplate, 2-20 impulses (mean value 4.3±1.2) needed. Vestibulomyringopexy was performed in 16 patients – as a first stage in 6 patients, as a second stage in 9 patients, and as a third stage in 1 case. Vestibuloincudopexy was performed in 9 patients – as a first stage in 3 patients and as second stage in 6 patients.

A choice of total or partial stapedectomy with installed on autovenous graft autocarti-lage prosthesis usage is determined by its high efficacy (ABG ‹ 10 dB in 96% cases) and long-lived results in patients with otosclerosis during 45 years [10,11,12].

To provide safe stapedectomy, a CO2 laser system (Lumenis, USA) with mirror hinge manipulator attached to the microscope was used; wave length (□) 10.6 □m. A CO2 laser system had an adopted to stapes surgery software that depending on focus distance and superimpulse diameter automatically provides effective and safe laser radiation duration and power. Howev-er, this software did not neglect thickness of laser impulse application area, but it provided for software parameters, influencing on laser impulse duration and power, change. Thus, we set up laser impulse individually, depending on stapes crus and footplate thickness and diameter of perforation; CO2 laser impulse duration changed automatically. Usage of flash scan for sta-pedotomy allowed safely hole formation in footplate by one or two impulses.

A surgery was performed intrameatally (intraauricularly) with local applying of 8.0 ml 2% solution of lidocaine and addition of 0.1% adrenaline hydrochloride solution (1:100000), using a stereomicroscope (Moller-Wedel GmbH, Germany). A tympanic cavity was opened widely due to usual autocartilage semiplate presence in tympanic membrane thickness deter-mining its rigidity. Absence of annulus fibrous during re-operations complicated this surgery stage. During tympanum cavity revision, a state of mucosa, some auditory chain elements mo-bility and presence, TSC areas character and localization and cicatrization processes, oval win-dow niche anatomical features, and additus and auditory tube isthmus state were evaluated.

To cross stapes crus a flash scan with superimpulse mode and focus distance 250 mm was used. Afterwards, stapes crus was crossed, and arch removed without footplate mobiliza-tion. In cases of instrumental stapes mobilization during its crus crossing, a footplate laser per-foration with individual matching of impulse diameter and power after grafts and oval window niche preparation, stapes was fully removed.

After removal of oval window frame mucosa and plastic materials preparation, a flash scan with superimpulse regimen and focus distance 250 mm were used for stapedotomy per-forming.

A footplate perforation was performed in its central part or closer to its posterior pole. A choice of perforation diameter depended on state of footplate and canal of n. facialis tympa-nal part.

After the footplate posterior pole instrumental removal, an autograft was applied on oval window frame; to predict occasional contamination of inner ear liquids and adhesive pro-cess development, an intimal part of autograft was turned to oval window side. These surgery stages were performed quickly to avoid blood penetration into oval window liquids that can re-sult in vestibulocochlear disorders development.

Beyong autovenous graft application, under lenticular process of incus long crus, or un-der a tympanic membrane, on autograft an autocartilage prosthesis was applied. At the end of surgery, for stapedial reflex restoration, a stapedius muscle tendon was placed at stapes pros-thesis.

After infusion of 0.2 ml dexamethasone solution into tympanum cavity, a meatotympa-nal graft was straightened on its previous place. A compulsory moment of this stage was hear-ing assessment with a "live" speech. At the end of surgery, silicone protectors were applied along the section line, and external auditory meatus was doughly tamponaded with microporous swabs with oxycellulose (Merocel) and antiseptic.

Patients' examination on surgery treatment and follow-up stages included endoscopy, otomicroscopy, and audiological tests. To evaluate efficacy of stapedoplasty techniques, tonal threshold audiometry (TTA) in the frequency range of 0.125 to 8 kHz as a method of air con-duction (AC) and bone conduction (BC) by clinical audiometer MA-31 (Germany) in sound-isolated camera was performed. TTA was carried out before surgery, then – before discharge, and three more times – in 1, 6, and 12 months after surgery. Pathomorphological assessment of removed TSC complexes were performed in 16 cases during two stages of reconstructive sur-geries. A study data statistical evaluation was carried out by applying an analysis of variance and Student test evaluation by computer programs Microsoft Excel and SPSS 17.0. The follow-up period lasted from 1 to 5 years. Ethics committee approved all stages of this study. Written informed consent was obtained from patient who participate in this study.

3. Results

After the first reconstructive stage, all patients had thin tympanic membrane with TSC complexes in its thickness or with autocartilage semiplate in membrane's center or posterior quadrants, when otomicroscopy (Figure 4).

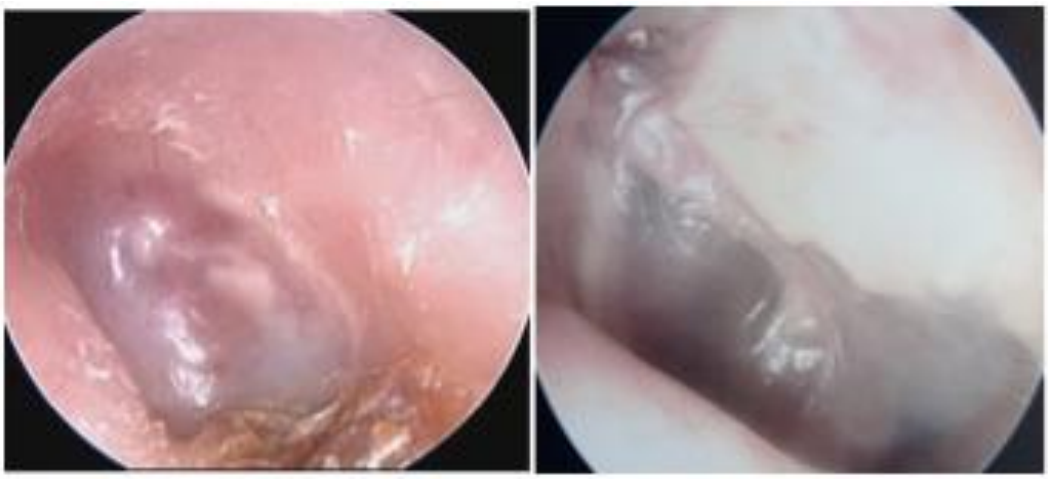

Figure 4. Endopicture of tympanic membranes in patients with TSC before stapedoplasty.

Histological evaluations during reconstructive surgery stages had shown that tympanic membrane integrity restoration provided decrease in inflammatory processes and TSC areas character changes due to tympanum cavity isolation; auditory tube functions and middle ear aeration improvement. This is responsible for necessity of stapedoplasty performing and appli-cation of stapes prosthesis on closing oval window autovein, to predict cochlear complications, not less than in a 12 months after the first reconstructive stage carrying out.

Analysis data of ABG mean values (35.8±6.4 dB before surgery) in TSC1 group showed their decrease in 1 month up to 27.1±7.3 dB; in 6 months – up to 18.3±8.3 dB, and in 12 months – up to 13.3±9.2 dB (Figure 5).

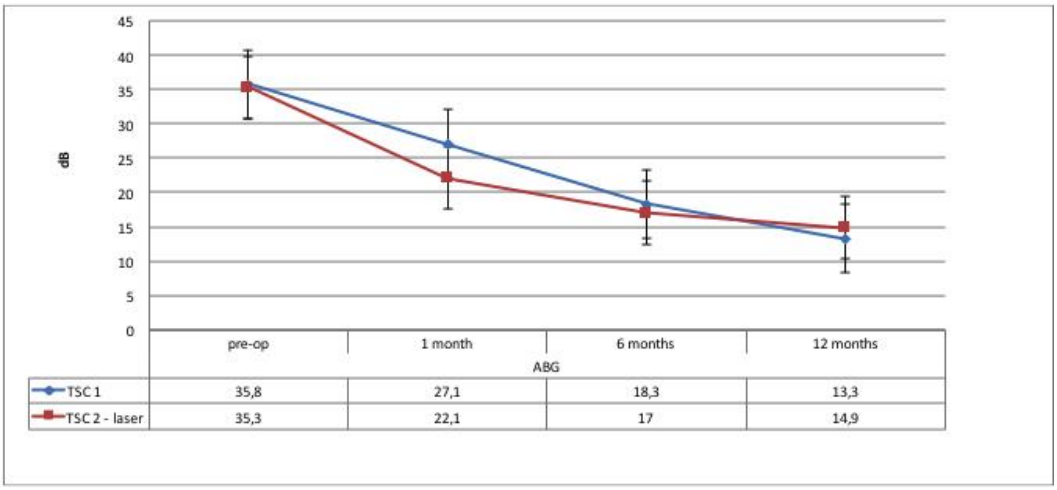

Figure 5. ABG mean values dynamics graph in both TSC groups.

Hence, instrumental stapedoplasty was effective during whole follow-up period, but its best efficacy was determined in 12 months after surgery. ABG values ‹ 20 dB were reached in 71.4% patients; from 20 to 30 dB – in 85.7%, and 30 dB – in 100% patients. Analysis data of auditory threshold by BC values (36.8±5.4 dB before surgery) showed their decrease in 1 month after surgery up to 44.1±5.5 dB; in 6 months – up to 17.0±8.0 dB, and in 12 months – up to 28.2±2.1 dB determined by inner ear reaction on surgery treat-ment.

Analysis data of ABG mean values (35.3±8.6 dB before surgery) in TSC2 group showed their decrease in 1 month up to 22.1±9.5 dB; in 6 months – up to 17.0±8.0 dB, and in 12 months – up to 14.9±7.4 dB. Stapedoplasty with laser assistance was effective during whole follow-up period, but its best results were shown in 6-12 months after surgery. ABG values ‹ 20 dB were reached in 76% patients; from 20 to 30 dB – in 92%, and 30 dB – in 100% patients. Analysis data of auditory threshold by BC values (30.3±11.3 dB before surgery) showed their consisten-cy in 1 month after surgery – 31.1±13.2 dB; in 6 months – 28.9±13.1 dB, and in 12 months – 28.3 ± 12.8 dB.

However, there was no difference found between functional results in speech frequencies range after cartilage prosthesis application under incus long process or under tympanic membrane (Figure 6).

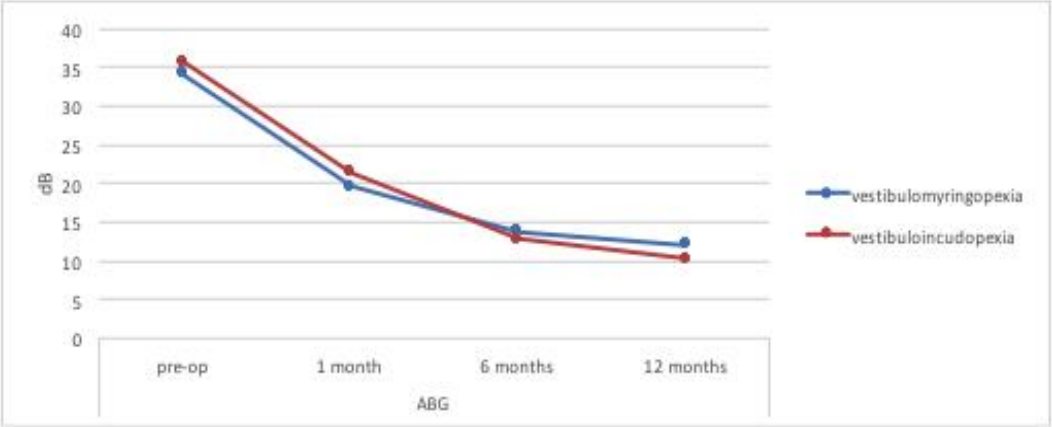

Figure 6. ABG mean values dynamics graph in TSC2 group after surgery regarding on stapedoplasty type.

4. Discussion

Stapes surgery (mobilization, stapedotomy, and stapedectomy) efficacy in TSC with decrease in ABG ‹ 20 dB can be reached in 25-87.5% cases (Table 3).

As well, best results are observed after stapedotomy (37.5-78%) and stapedectomy (25-87.5%) vs. stapes mobilization (30.8-72%) [1-3,5,13-18].

Last decade, a BC thresholds increase after stapes surgery in patients with TSC occurs in 4-10.6% cases; more frequently in stapedoplasty than in stapes mobilization (14.3% vs 8%) [1,2,5,18]. However, many authors do not mention inner ear negative reaction after stapedoplasty in patients with TSC when staging, carefulness, and patients' rigorous selection [2,4,9,14,17,19,20]. This is why stapedoplasty in TSC should be performed not less than in a year after successful tympanoplasty when enclosed tympanum cavity and normal mucosa form, and auditory tube functions recover [1,3,5,21,22].

Piston stapedoplasty (stapedotomy) is a preferable surgery technique in tympanosclerot-ic stapes fixation, due to inner ear minimal traumatization and performance facility. In cases of intact ossicular system, stapedoplasty can be performed in a classic or in a "backspace" manner with stapes prosthesis fixation on incus. In other cases, piston prosthesis fixation is realized by a handle of malleus or by a prepared foot (neomalleus) situated in the tympanic membrane thickness. In the after-surgery period, there is an evidence of ABG decrease ‹ 10 dB in 20-39% patients and ‹ 20 dB in 37.5-78% patients [1,2,3,5,7,13,16,18,20,23].

In cases of TSC, stapedectomy is not a preferable technique for hearing loss treatment [15,24]. However, due to technical difficulties, about 20% of planned stapedotomies are result in stapedectomies [7]. In stapes TSC fixation, stapedectomy with different prosthesis (under incus, malleus handle, or neomalleus) usage allows to reduce ABG up to 10 dB in 25-45% patients and up to 20 dB – in 25-87.5% patients [1,3,14,16,17,19,25,26]. In this case, a prosthesis applies on the autovenous graft (vein, fascia, adipose tissue, or perichondrium) that closes the oval window.

Comparing different stapedoplasty techniques results in patients with tympanosclerotic stapes fixation, some authors refer to stapedectomy and prosthesis application on a graft ad-vantages versus piston technique performing in the long-term follow-up period [3,14,,19,]. Con-trary, another data show stapedoplasty less efficacy when stapes prosthesis fixation on malleus handle versus fixation on an incus long crus [8,13,16]. Several studies data did not find any sig-nificant differences in surgery efficacy, depending on its technique, materials, and stapes pros-thesis fixation type [1,5,17,27].

Some investigators testify for better functional results in stapedotomy with laser assis-tance and microdrill usage versus instrumental technique [1,5,18,28]. Comparing CO2 laser and microdrill imply for calibrated stapedotomy on inner ear function, in the early follow-up peri-od, its transient depression is evaluated [29].

Table 3. Efficacy of different stapes surgery techniques in patients with TSC

Authors	Year	Surgery techniques	n	Follow-up period duration	Efficacy (ABG ‹20 dB)	BC increase › 10-20 dB

Sheehy J., Crabtree J.	1973	Stapedectomy	32	6 yrs	60%	deafness in 6.3%
Kinney S.	1978	Mobilization Stapedectomy	60	-	-	8% 26%
Gormley P.	1987	Piston method Stapedectomy	6 61	5 yrs	72%	deafness in 4.5%
Tos M. et al.	1990	Mobilization Stapedectomy	73	1-15 yrs	60% 25%	-
Gidding N., House J.	1992	Mobilization Stapedectomy	102 40	5 yrs	‹10 dB 45% ‹ 20 dB 72%	-
Teufert K., De La Cruz A.	2002	Mobilization Stapedectomy	53 20	0.5-1 yrs	60%	-
Vincent R. et al.	2002	Piston method Stapedectomy+TORP	19 45	0.5-7 yrs	‹10 dB 39% ‹ 20 dB 70%	8%
Berenholz L., Lippy W.	2004	Piston method	10	1.5 yrs	‹10 dB 20% ‹ 20 dB 60%	-
Yang S. et al.	2005	Mobilization Stapedotomy Stapedectomy	119	0.5-5 yrs	30.8% 62.5% 43.1%	-
Yetiser S. et al.	2007	Mobilization + PORP Stapedectomy+TORP	5 7	4.3 yrs	33%	NA
Kizilkaya Z. et al.	2008	Mobilization Piston method	23 8	2 yrs	47.8% 37.5%	NA
Al-Qahtani M., Hagr A.	2008	Stapedectomy	8	0.5 yrs	87.5%	NA
Çelik H. et al.	2008	Stapedotomy Stapedectomy+TORP	8 17	0.5-10 yrs	65-71%	8%
Stankovic M.	2009	Stapedectomy	12	-	50%	NA
Chernushevich I.I.	2012	Piston method Stapedectomy+TORP	26 9	3 mo-2 yrs	78% -	-
Querat C. et al.	2012	Piston method Stapedectomy+TORP	28	0.5-3 yrs	50-67% 43-68%	NA
Khorsandi-Ashtiani M. et al.	2014	Mobilization Stapedectomy+TORP	38 28 (66)	3 yrs	50.9% 71.4% (63.6%)	7.9% 14.3% (10.6%)
Zaugg Y., Linder T.	2015	Stapedotomy	23	2-42 mo	73%	4%

Yrs – years; mo – months; NA – data are not available.

Hearing loss treatment results insecurity in this pathology is common and occurs due to un-dertreated inflammatory processes and lack of blood supply. Most surgeons tell about de-crease in stapedoplasty functional results in TSC (from 50.3% in 6 months after surgery to 34.5% in 5 years) while increase in follow-up period duration [1,16,27]. Contrary, another data show good results even in long-term follow-up period, evidencing hearing improvement up to 10 years [2,15].

Our results are similar to these of stapedoplasty efficacy studies in patients with TSC. This type of technique is more safe when laser assistance and vestibular liquids isolation. How-ever, partial stapedectomy, with stapes autocartilage prosthesis application on venous graft in patients with TSC, results are significantly worse than these in otosclerosis patients; these data are evi-denced by another study results, as well [23]. Our stapedoplasty with laser assistance re-sults in TSC patients do not show BC thresholds increase in 10-15 dB that is found in 81-83% otosclerosis patients [30,31].

5. Conclusions

In sum, to predict after-surgery cochlear complications after stapedoplasty in TSC pa-tients, it is necessary to notice undertreated inflammation conditions and to isolate vestibule by autotis-sue. Stapedoplasty with stapes autocartilage prosthesis application is effective with ABG decrease ‹ 20 dB in 73.7% TSC patients. Laser assistance during stapes crus crossing stage and stapedotomy in the early follow-up period results in absence of inner ear reaction for surgery; moreover, ABG mean values decrease more rapidly than these during instrumental surgery technique.

Application of artificial intelligence:

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

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

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Article

Assessing the Learning Curve in Contact Endoscopy for Oral and Oropharyngeal Examination

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Citation Chuchueva N., Cherenkova V., Svistushkin I. Assessing the learning curve in contact endoscopy for oral and oropharyngeal examination. Otorhinolaryngology, Head and Neck Pathology (ORLHNP). 2023; 2 (4): 57-61.

https://doi.org/10.59315/ORLHNP.2023-2-4.57-61

Academic Editor: Valentin Popadyuk

Received: 13.12.2023
Revised: 20.12.2023
Accepted: 01.01.2024
Published: 30.01.2024

Abstract: The early and accurate detection of oral and oropharyngeal malignant lesions is crucial, impacting both treatment outcomes and patient prognosis. Contact endoscopy is one of the prospective methods in this respect. However, the integration of contact endoscopy into routine clinical practice is not without challenges. It requires specific skills and expertise for both performing the procedure and interpreting the enhanced mucosal images (the type of vascular patterns).
We conducted a prospective analysis over a 9-month period, involving otolaryngologists (n=18) at various stages of their careers. To assess the learning curve, we evaluated both the technical proficiency and diagnostic accuracy of participants at multiple time points: at baseline, 1 month after initial training, and at 3, 6, and 9 months.
At baseline, the average time to complete a contact endoscopy procedure was 180.7 seconds for the more experienced investigator and 185.7 seconds for the less experienced investigator, reducing to 120.2 seconds and 123.2 seconds at the 9-month assessment, respectively. Image clarity also improved, with only 34.5% of initial images deemed 'high quality', increasing to 94,5% after 9 months for more experienced investigator. The correct interpretation of the contact endoscopy findings did not depend much on the number of high-quality images.

Keywords: contact endoscopy, oral cavity malignant neoplasms, curve assessment

1. The purpose of the study

The early and accurate detection of oral and oropharyngeal malignant lesions is crucial, impacting both treatment outcomes and patient prognosis. Despite visually accessible localization, oropharyngeal and oral cavity malignant neoplasms are diagnosed in the later stages in 60% of cases, resulting in a high mortality rate and a low quality of life [1]. The standard evaluation of the oral cavity and oropharynx is a conventional oral and oropharyngeal examination without the use of additional research methods [2], that does not always allow to verify changes in the mucous membrane specific for an early dysplastic process. Thus, the search for additional minimally invasive and still effective diagnostic methods that can be used in the routine practice remains very important.

Contact endoscopy [3, 4] is one of the prospective methods in this respect. This technique involves the direct application of a magnifying endoscope to the mucosal surface, has been increasingly recognized for its ability to provide high-resolution images of superficial oral and oropharyngeal lesions [5-7]. This technique allows for the in vivo observation of microvascular patterns [5] and cellular structures [6, 8, 9], facilitating the differentiation between benign and malignant lesions with greater precision [3, 6, 10, 11].

However, the integration of contact endoscopy into routine clinical practice is not without challenges. One significant barrier is the learning curve associated with the technique. Unlike conventional endoscopic methods, contact endoscopy requires specific skills and expertise, particularly in interpreting the enhanced mucosal images (the type of vascular patterns) [5]. The proficiency in contact endoscopy is not merely a function of technical ability but also hinges on the clinician's interpretative acumen, developed through extensive training and experience.

The learning curve in contact endoscopy for oral and oropharyngeal examination has not been comprehensively studied. Understanding this learning curve is essential, as it may directly impacts

the diagnostic accuracy and effectiveness of the technique in clinical settings and gives the understanding what period is required for the investigator to get the best diagnostic result [12]. This paper aims to fill this gap by evaluating the learning process of medical professionals in using contact endoscopy for the oral and oropharyngeal examination. By delineating the learning curve, we aim to provide insights into the training needs for otolaryngologists, ultimately enhancing the diagnostic capabilities in oral and oropharyngeal pathology detection.

2. Materials and methods

Study Design and participants

This observational study was designed to assess the learning curve associated with contact endoscopy during oral and oropharyngeal examination. We conducted a prospective analysis over a 9-month period, involving otolaryngologists at various stages of their careers, from just graduated after the residency doctors to experienced doctors who have already been familiar with other endoscopic technique, however without any expertise in contact endoscopy.

Participants (n=18) were recruited from one tertiary care center specializing in otolaryngology. Inclusion criteria for otolaryngologists were: (1) a valid medical and otorhinolaryngological license, (2) at least one year of experience in otolaryngology, and (3) no prior experience with contact endoscopy. Informed consent was obtained from all participants. The study also involved healthy volunteers undergoing routine screening program for the oral and oropharyngeal pathology detection, with the consent obtained for the use of contact endoscopy and data recording. The study was approved by the Institutional Review Board (protocol number 04/2020). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

Training Protocol

A standardized training program was developed, comprising theoretical component. The theoretical component included didactic sessions on the principles of contact endoscopy, interpretation of vascular patterns, and differentiation of benign from malignant lesions [5]. Contact endoscopy was performed using ANDREA/DIAS Contact Micro-Laryngoscope, with HOPKINS® straight forward telescope 0° with 5.5 mm in diameter and 23 cm in length (Karl Storz, Tuttlingen, Germany).

Evaluation of Learning Curve

To assess the learning curve, we evaluated both the technical proficiency and diagnostic accuracy of participants at multiple time points: at baseline, 1 month after initial training, and at 3, 6, and 9 months. Technical proficiency was measured based on the time taken to complete an examination, the clarity of images obtained, and the ease of equipment handling. Considering that the investigation was done in the circumstances of screening evaluation, the "diagnostic accuracy" was assessed by comparing the revealed by the participants and actual type of the vascular pattern. So, the number of correct interpretations were counted and reported as a percentage.

Each participant is expected to perform a minimum of 5 contact endoscopy procedures per month to gain practical experience. This number is chosen to ensure that each participant has enough practice to improve their skills while not overwhelming them with the study requirements or interfering with patient care. It means that by the 3 months' time point the participants performed at least 15 procedures, for the 6 months' time point – 30 procedures and for the 9 months' time point – 45 procedures.

Data Collection

Data were collected on a standardized form, including details of each contact endoscopy procedure, such as duration, image quality, and diagnostic findings. Additionally, feedback from participants regarding their confidence and perceived proficiency with the technique was gathered through structured questionnaires.

"High-Quality Images" refers to the clarity and diagnostic usefulness of the images obtained through the contact endoscopy procedure. We considered the following criteria: (1) Clarity and Resolution: the images should be clear with high resolution, allowing for detailed visualization of the mucosal surface as allowing to distinguish subtle differences in vascular patterns. (2) Focus and Magnification: the images should be well-focused and properly magnified to reveal the necessary details of the mucosal surface and vascular structures. (3) Absence of Artifacts: high-quality images are free from artifacts such as blurring, shadows, or distortions that can obscure details and hinder accurate diagnosis. We assessed every criteria binary yes/no and classified the image as "high quality" in case of all three criteria gained "yes". In our study, the percentage of

high-quality images is used as a metric to assess the technical proficiency of the medical professionals in conducting contact endoscopy. An increase in this percentage over time indicates an improvement in the ability of the practitioners to effectively use the contact endoscopy equipment and techniques to produce diagnostically useful images.

3. Results

Participant Demographics

The study included 18 otolaryngologists (10 males, 8 females) with varying levels of experience but new to contact endoscopy. Their experience ranged from 1 to 15 years in otorhinolaryngology. Participants considered as "more experienced" have been using any type of endoscopes for more than 5 years of practice. All participants completed the theoretical and practical components of the training program. All the volunteers did not have any evident pathologies of the oral cavity and oropharynx. The contact endoscopy was performed on an outpatient basis without any prior anesthesia. The patient was in sitting position with opened mouth. The endoscope was introduced into the oral cavity, then its tip was placed on the mucosa of the following anatomical zones in sequence: the floor of the mouth, buccal mucosa bilaterally, retromolar trigone bilaterally, and anterior tonsillar arch bilaterally.

Technical Proficiency Assessment

Technical proficiency, assessed by examination duration and image quality, showed significant improvement over time (Table 1). At baseline, the average time to complete a contact endoscopy procedure was 180.7 seconds for the more experienced investigator and 185.7 seconds for the less experienced investigator, reducing to 120.2 seconds and 123.2 seconds at the 9-month assessment, respectively. Image clarity also improved, with only 34.5% of initial images deemed 'high quality', increasing to 94,5% after 9 months for more experienced investigator. Less experienced investigators got high quality images at baseline in 20% of cases, increasing to 84,7% after 9 months. The correct interpretation of the contact endoscopy findings did not depend much on the number of high-quality images.

Table 1. The value of the assessed parameters

	More experienced investigator			Less experienced investigator		
Parameter	Average time, sec.	High quality images, %	Correct interpretation of vascular pattern, %	Average time, sec.	High quality images, %	Correct interpretation of vascular pattern, %
Baseline	180,7± 1,8	34,5	63,6	185,7± 0,7	20,0	48,6
3 months	159,9± 1,4	43,6	90,8	164,0± 2,6	31,4	87,5
6 months	140,4± 1,9	67,8	97,5	145,4± 1,9	52,3	93,3
9 months	120,2± 1,0	94,5	99,4	123,2± 1,2	84,7	98,1

Subgroup Analysis

Subgroup analysis revealed that prior experience in endoscopic technologies application positively correlated with the speed of acquiring proficiency in contact endoscopy. Experienced in endoscopy otorhinolaryngologist reached a plateau in technical proficiency by the 3-month mark, while less experienced practitioners took 6 months in average. Sufficient number of correctly revealed vascular patterns for both more and less experienced doctors was gained by the 3-month time point (20 procedures).

Participant Feedback

Feedback collected from participants indicated an increase in confidence in using contact endoscopy over time. Initially, only 40% of participants felt confident in their ability to use the technique effectively; this number increased to 90% by the end of the study.

Challenges and Limitations

Participants reported challenges in the initial stages, particularly related to handling the endoscope and interpreting the enhanced images. At the same time, participants who were experienced in the use of any type of rigid and flexible endoscopes. The study's limitations include its reliance on self-reported data for some measures and the potential variability in patient cases.

4. Discussion

Interpretation of Findings

The findings of our study indicate a significant learning curve associated with the use of contact endoscopy in the examination of oral cavity and oropharynx. The improvement in both the technical proficiency, as evidenced by the reduction in examination duration and the increase in high-quality image acquisition, and the diagnostic accuracy over the 9-month period underscores the importance of structured training and continued practice.

Comparison with Existing Literature

There is no data in the literature about the learning curve assessment in contact endoscopy for oral and oropharyngeal examination. At the same time, there is data considering narrow band imaging that have some similarities with contact endoscopy, at least in case of vascular pattern interpretation. Dias-Silva et. al. reported that from the first to the last 50 videos, a learning curve was observed with a 10% increase in global accuracy. And after 200 videos, specificity for dysplasia was greater than 95%. The videos were delivered to the participants through the specially designed web-based learning system [13]. Zurek et.al. reported that a minimum of 65 narrow band imaging examinations are required to reach a plateau phase of the learning process in assessment of glottis lesions [14].

Our results align with existing literature that emphasizes the importance of experience and training in mastering endoscopic techniques. Studies in similar fields have also reported initial challenges in adopting new diagnostic technologies, gradually overcoming them with practice and experience. The positive correlation between prior endoscopic experience and a steeper learning curve in our study adds to the growing body of evidence that pre-existing procedural skills can facilitate the acquisition of new techniques.

Clinical Implications

The marked improvement in the percentage of the correctly detected vascular pattern suggests that with adequate training, the diagnostic accuracy of the method might be improved. At the same time it might become a topic of the further investigations. This is particularly relevant in early detection of malignancies, where contact endoscopy can complement conventional oral and oropharyngeal examination, potentially leading to earlier intervention and improved patient outcomes.

The study highlights the necessity for comprehensive training programs in contact endoscopy for otolaryngologists. Given the steep learning curve, especially for practitioners with less prior experience in any type of endoscopic evaluation, tailored training programs with a balance of theoretical knowledge and practical skills are essential. Additionally, the study suggests that continuous practice and exposure are crucial for maintaining and improving proficiency.

Limitations of the Study

While our study provides valuable insights, it is not without limitations. The reliance on self-reported measures for some assessments, such as image quality, might introduce subjectivity. Furthermore, the variability in patient cases could affect the generalizability of our findings. Future studies could involve a larger and more diverse participant pool and incorporate more objective measures of image quality and diagnostic accuracy.

Future Research Directions

Further research could focus on long-term outcomes of contact endoscopy training, exploring how sustained practice impacts diagnostic proficiency. Additionally, studies comparing different training methodologies could provide insights into the most effective approaches for teaching this technique. For instance, there is data in the literature about YouTube-based learning program that was feasible for training process [15]. The exploration of patient outcomes as a function of contact endoscopy use in diagnosis would also be valuable.

5. Conclusion

Our study provides an analysis of the learning curve associated with contact endoscopy for the oral and oropharyngeal examination. The findings highlight the important role of structured training and continuous practice in mastering this technique. Over the 9-month study period, improvements were observed in both technical proficiency and diagnostic accuracy among participating otolaryngoloegists. These improvements were particularly pronounced in those with prior experience in endoscopic investigations, suggesting that pre-existing endoscopic skills can facilitate the acquisition of proficiency in contact endoscopy. The reduction in examination duration and the increase in the production of high-quality images are indicative of the growing technical adeptness of the participants.

Our study also underscores the importance of training in adopting new medical technologies. Given the observed learning curve, it is imperative for medical institutions to invest in training programs that not only introduce contact endoscopy techniques but also provide ongoing support and learning opportunities for practitioners.

Despite these promising findings, the study acknowledges certain limitations, including the potential for subjective bias in self-reported measures and the variability in patient cases. These factors highlight the need for continued research, particularly studies that employ more objective assessment tools and involve a more diverse range of clinical settings and patient populations.

Application of artificial intelligence:

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

Funding: The authors have no funding, financial relationships, or conflicts of interest to disclose.

Institutional Review Board Statement: This study protocol was reviewed and approved by the Academy Review Board (protocol number 04/2020).

Informed Consent Statement: Subjects have given their written informed consent before proceeding for the clinical examination.

Conflicts of Interest: The authors have no conflicts of interest to declare. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Article

Triphasic Pulse Stimulation Pattern in Cochlear Implant Users Assessed with Ecap Measure

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Abstract: The rationale for the use of three-phase stimulation for programming the processor of the cochlear implantation system (CI) in patients with deafness is presented. To study the possibilities of using a new type of stimulation, we selected patients after cochlear implantation, with signs of facial nerve stimulation (FNS) in postoperative period. All subjects were previously fitted with an audio processor with individual fitting maps based on traditional biphasic stimulation. The use of three-phase stimulation to prevent FNS is caused by the geometry of the electric current pulses, which allows to reduce the penetrating power of the charge in the tissues and eliminate the effect on the facial nerve, without resorting to reducing the levels of stimulation necessary to create a dynamic range of sound perception. Comparative data of the parameters and the results of audiological testing in 21 patients with symptoms of FNS with traditional (two-phase) and three-phase electrical pulses in the stimulation algorithm of the CI system are presented. The positive effect of three-phase stimulation has been established. The results of the study show a significant increase in sound perception indicators when switching to a three-phase stimulation algorithm.

Keywords: cochlear implantation, hearing and speech rehabilitation, sensorineural hearing loss, cochlear implant processor fitting.

Citation: Pashkov A., Voevodina K., Popadyuk V., Pashkova A., Naumova I., Izosimov A., Klyachko D. Triphasic Pulse Stimulation Pattern in Cochlear Implant Users Assessed with Ecap Measure. Otorhinolaryngology, Head and Neck Pathology (ORLHNP). 2023; 2 (4): 62-66.

https://doi.org/10.59315/ORLHNP.2023-2-4.62-66

Academic Editor: Valentin Popadyuk

Received: 13.12.2023
Revised: 20.12.2023
Accepted: 01.01.2024
Published: 30.01.2024

1. Introduction

Facial nerve stimulation (FNS) is one of the possible complications of cochlear implantation (CI). According to the literature, this condition occurs in 1-15% of patients in the postoperative period [2, 3]. FNS can be mild, affecting only individual facial muscles (e.g., eye, mouth, or forehead), or severe, when contractions affect all facial muscles and cause pain [4].

FNS can manifest immediately after CI activation or with a delay; a case with FNS onset 10 years post-activation has been described. Initial symptoms may not be obvious but worsen over time and depending on audio processor settings, leading to patient complaints and clinical manifestation [5]. Moreover, the evaluation of initial FNS symptoms is largely subjective, therefore It is important not to miss the initial manifestation of FNS in young children and people with neurological comorbidities.

The causes of FNS include: a) proximity of the facial nerve to the outer wall of the cochlea, b) excessively high stimulation levels in combination with auditory nerve hypoplasia or after a long period of deafness, and c) decreased bone impedance due to otosclerosis, meningitis, or temporal bone fracture [6, 7].

Traditionally, CI audio processors use biphasic pulse stimulation. Two common ways of reducing FNS when using the biphasic mode are: a) switching off individual electrode channels and b) reducing the maximum comfortable loudness (MCL) level. However, these interventions harm speech perception and limit the duration of CI use. An alternative solution that does not have these limitations is triphasic pulse stimulation [8].

Biphasic pulse stimulation has two phases with opposite polarities but with the same duration and amplitude - one negative (cathode) and one positive (anode) [5]. Triphasic pulse stimulation has two phases with the same polarity, duration, and amplitude (cathode) and one phase with the opposite polarity, double the duration, and the same amplitude (anode), resulting in a balanced charge [5]. It is suggested that triphasic stimulation prevents current spread into neighbouring tissues and thus reduces FNS, even though it requires higher stimulation levels than the biphasic mode to achieve the same MCL levels [5].

Problem: hearing is compromised if FNS is treated with conventional methods. Triphasic stimulation provides an alternative solution. Need evidence that speech understanding improves (no change in Braun 2019 paper).

Aims: The aim of the study was to evaluate the effectiveness of this method in treating FNS and effect of changing the stimulation type from biphasic to triphasic on speech intelligibility in quiet and noise.

2. Patients and Methods

Participants were recruited from CI users treated at the Research Institute of Pediatrics and Child Health of the Central Clinical Hospital of the Russian Academy of Sciences and at the Research Institute of Ear, Throat, Nose, and Speech in St Petersburg. All participants had a CI system from MED-EL (Austria) that allowed to choose between two stimulation types: a biphasic and triphasic pulse. Participants were excluded if they had neurological comorbidities or congenital anatomical anomalies of the cochlea. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Central Clinical Hospital of the Russian Academy of Sciences.

Fitting:Prior to the study, all participants had speech processors fitted with the biphasic pulse stimulation and had clinical manifestations of FNS (contraction of 1 or more facial muscles) during fitting or speech testing. Their FNS-related discomfort was initially managed by lowering the MCL level and adjusting the microphone gain. The participants demonstrated unsatisfactory auditory performance when tested by a speech therapist despite regular speech rehabilitation sessions.

The MCL levels were measured during the fitting with the biphasic and triphasic mode on all electrode contacts. Electrically evoked compound potentials (ECAPs) were measured on all electrode contacts using the AutoART tool of the MAESTRO software (version 7), MED-EL, Austria).

Audiological testing:Speech intelligibility was assessed using the standardized Russian pediatric multisyllabic speech test at three time points: before the triphasic mode activation (using the biphasic mode), 1 hour post-activation, and 48 hours post-activation. The speech intelligibility in quiet test was administered at 65 dB SPL in free field from zero degrees azimuth. The speech intelligibility in noise test was administered under the same conditions at 6 dB SNR, with both the signal and the noise sources located at zero degrees azimuth (S0N0).

The whispered voice test was conducted at two time points: before the triphasic mode activation (using the biphasic mode) and 1/48 hours post-activation. Each participant was seated while the examiner stood behind them to prevent lip reading. The examiner whispered words at different distances from the participant and the participant repeated them. The maximum distance at which the participant correctly repeated 50% of whispered words was recorded.

Data analysis:Descriptive statistics (mean, standard deviation, and range) were calculated for the demographic and audiological data. The Kolmogorov-Smirnov test and the Shapiro-Wilk test were used to check if the data were normally distributed. The Friedman test was used to assess the change in speech intelligibility across all three conditions (biphasic, triphasic 1 h post-activation, triphasic 48 h post-activation). Pairwise comparisons were done using the Wilcoxon signed-rank test. A p-value ≤ 0.05 indicated statistical significance. For the speech intelligibility tests, the p-value was adjusted to ≤ 0.017 using the Bonferroni correction for multiple comparisons. Statistical analysis was done in IBM SPSS Statistics (version 25, IBM, Armonk, New York, USA).

3. Results

Demographics:21 CI users included in the study were 3 to 12 years old (mean age: 6.0 ± 1.98 years old). The mean age at implantation was 10.0 ±16.34 months old (range: 6 – 75 months old). The mean time of CI use with biphasic pulse stimulation was 36.0 ± 21.02 months (range: 1 – 112 months).

Fitting:The electrode array insertion was complete and all electrode contacts were activated in all participants.

Speech Intelligibility:Participants' speech intelligibility in quiet improved significantly after the triphasic mode activation (Friedman test: Chi-square = 29.585, df = 2, $p < 0.001$). Individual pairwise comparisons using the Wilcoxon signed-rank test confirmed the statistically significant improvement. The mean score increased from 41.9% (SD = ±25.3%) pre-activation to 51.1% (SD = ±21.5%) 1 h post-activation ($z = -2.447$, $p = 0.014$) and to 76.0% (SD = ±19.3%) 48 h post-activation (vs biphasic: $z = -3.884$, $p < 0.001$; vs 1 h post-activation: $z = -4.016$, $p < 0.001$). The distribution of scores is presented in Figure 1.

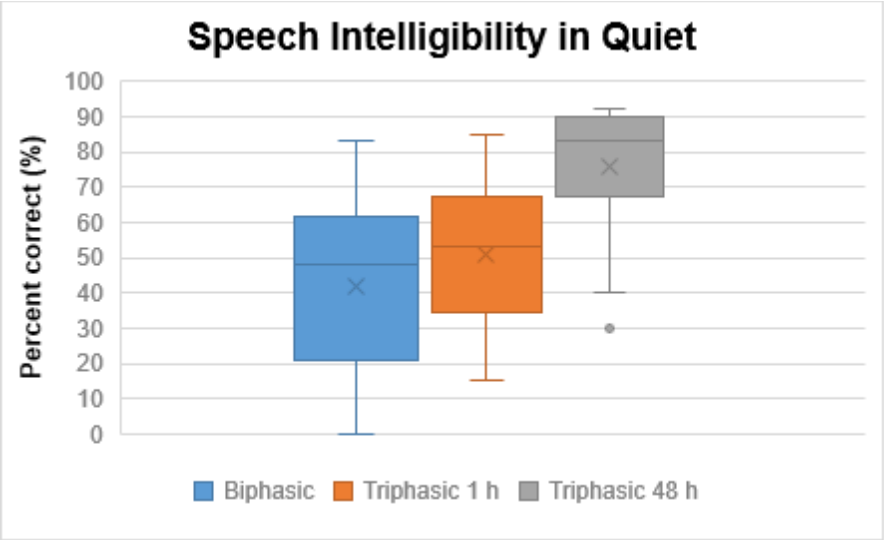

Figure 1. Speech intelligibility in quiet (% of correct responses) was assessed with the biphasic mode (blue) and with the triphasic mode 1 hour (orange) and 48 hours post-activation (gray) across 21 participants.

Participants' speech intelligibility in noise improved significantly, too (Friedman test: Chi-square = 28.617, df = 2, $p < 0.001$). Pairwise comparisons were also statistically significant. The mean score increased from 37.4% (SD = ±25.2%) pre-activation to 51.8% (SD = ±22.9%) 1 h post-activation ($z = -3.583$, $p < 0.001$) and to 68.0% (SD = ±20.8%) 48 h post-activation (vs biphasic: $z = -3.911$, $p < 0.001$; vs 1 h post-activation: $z = -3.924$, $p < 0.001$). The distribution of scores is presented in Figure 2.

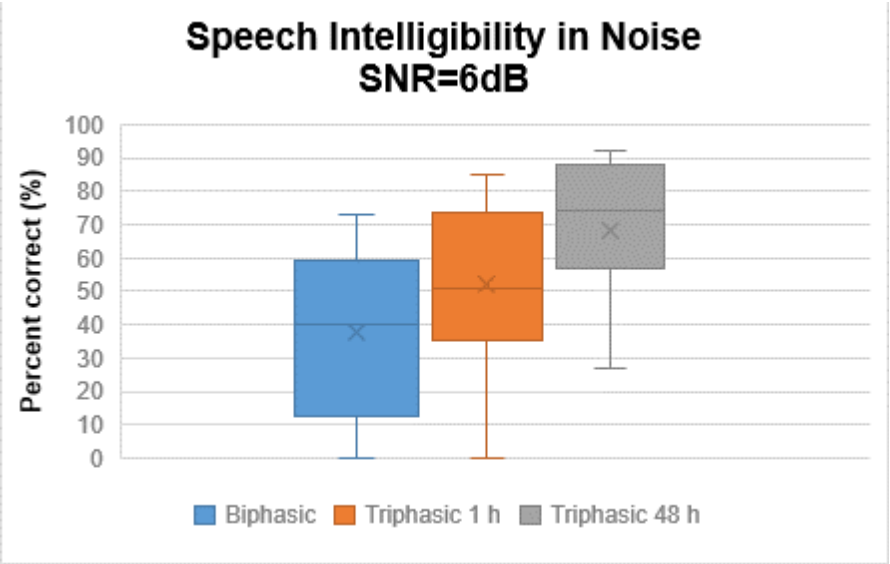

Figure 2. Speech intelligibility in noise (% of correct responses, signal-to-noise ratio = 6 dB) was assessed with the biphasic mode (blue) and with the triphasic mode 1 hour (orange) and 48 hours post-activation (gray) across 21 participants.

Whispered Voice Test:The average performance in the whispered voice test improved across participants from the average distance of 3.6 m (SD = ±0.9 m) to 5.6 m (SD = ±0.5 m) and this change was statistically significant (Wilcoxon signed-rank test: $z = -3.912$, $p < 0.001$). Individual performance improved in all but two participants (P7 and P15, Fig. 3).

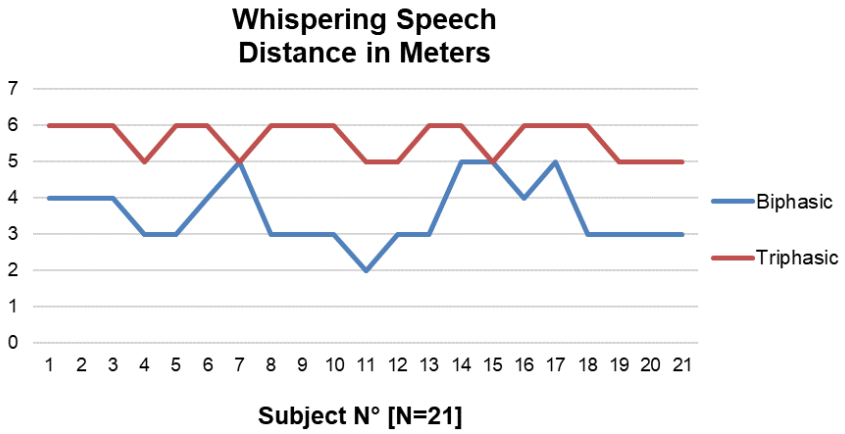

Figure 3. Individual results of the whispered voice test across 21 participants using the biphasic mode (blue) and the triphasic mode (orange).

ECAPs and Maximum Comfortable Loudness Levels:MCL levels were measured with the biphasic and triphasic modes on. The average MCL levels correlated with the ECAP values across electrode channels both in biphasic (stats) and triphasic mode (stats) (Fig. 4).

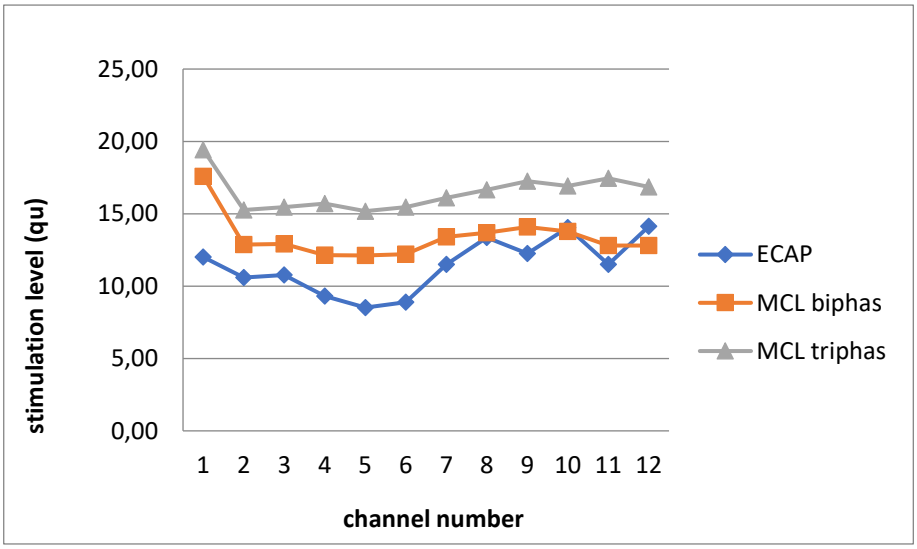

Figure 4. ECAP values (blue) and MCL levels across electrode channels in biphasic (orange) and triphasic mode (grey).

4. Discussion

The use of three-phase stimulation positively affects the rehabilitation of patients after CI having manifestations of stimulation of the auditory nerve due to a relatively larger dynamic range of sound perception. The relationship of MCL values in both biphasic and three-phase stimulation with ECAP registration thresholds was statistically significant, suggesting the potential of this solution, regardless of the type of stimulation chosen, since ECAP thresholds correlate with MCL [9]. The increase in MCL values required to create an effective dynamic range, with three-phase stimulation, can prevent the occurrence of FNS manifestations, as previously shown [8] in a study using electromyography in patients under general anesthesia. Our study shows the positive effect of three-phase stimulation while simultaneously increasing MCL levels on the results of speech testing or speech audiometry (in two patients with advanced speech skills). Three-phase pulses reduce the manifestations of FNS by distributing the charge between two negative phases of the same duration and one positive phase with twice the duration. The results of speech testing and speech audiometry (in children with developed speech skills) showed a significant increase in sound perception when switching to a three-phase stimulation algorithm.

5. Conclusions

The use of three-phase CI stimulation is a promising tool to prevent facial nerve stimulation after cochlear implantation while maintaining an effective dynamic range and, therefore, a rela-

tively large sound perception potential compared to the traditional biphasic stimulation algorithm. In case of clinical manifestations of FNS, it is recommended to use a three-phase type of stimulation to create fitting maps for patients with CI.

Application of artificial intelligence :

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

Acknowledgments. The authors would like to thank Angelina Gurkina (MED-EL) for her medical writing services on a version of this manuscript.

Author Contributions: A.V. Pashkov — concept and design of research, writing text I.V. Naumova — concept and design of research, collection and processing of material, statistical processing; A.E. Pashkova — collection and processing of material; K.I. Voevodina — collection and processing of material, visualization; A.A. Izosimov — editing; V.I. Popadyuk — editing, D.S. Klyachko— editing. All authors read and approved the final version of the manuscript before publication.

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

Our First Experience of Using Blue Light Laser for Endoscopic Endonasal Removal of Juvenile Angiofibromas

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Abstract: Background. Juvenile nasal angiofibroma (JNA) is a very rare benign lesion originating from the pterygopalatine fossa with distinctive epidemiologic features and growth patterns. The typical patient is an adolescent male with a clinical history of recurrent severe nasal bleedings and blockage the nose. Currently, even though surgery often caused severe operative bleeding, it is considered the ideal treatment for JNA. Refinement in preoperative embolization, which provides significant reduction of intraoperative bleeding. In spite of breakthrough of Endoscopic techniques which minimize the risk of residual disease, the search of new devises which can help to management of JNA is still continue in order to minimize the surgical complications. Laser methods as surgical treatment have been actively used in rhinology during the past decades. We purposed to summarize information about current lasers and their use in rhinology.

Aim. The purpose of the study is the literature review and to describe our experience of using new blue laser during JNA removal. Evaluation of advantages and disadvantages, determination of indications and limits of its use in rhinosurgery

Methods- A literature review from 2000 to 2022 using the PubMed database was employed. Keywords used included "laser surgery", "blue light laser", "photoangiolytic laser", "laser in rhinosurgery". The most up to date studies published for each rhinology condition that was treated with laser surgery was reviewed. Then endoscopic removal through the nose was performed. During the surgery TrueBlue laser was used to cut the tissues and coagulate injured vessels.

Results. Rhinological conditions appropriate for laser applications are discussed. There are related papers to a number of applications including hereditary hemorrhagic telangiectasia, rhinitis, turbinate surgery, dacryocystorhinostomy, septoplasty, choanal atresia, and sphenopalatine artery ligation, paying attention to the outcomes of the studies. It is the first experience of using blue laser in rhinosurgery and particulary ib removing JNA.

Conclusion. Intranasal laser surgery, despite the fact that interventions are performed almost bloodlessly, and often do not require nasal tamponade, indications for their performance are limited, due to deep burns of the nasal mucosa, and alteration of mucociliary clearance therefore lasers are not so often used in rhinology. The short-wave blue laser with a wavelength of 445 nm, used in Europe in oto- and laryngosurgery, may have some potential advantages in rhinosurgery, but the practical dataset are limited yet.

Keywords: angiofibroma, laser surgery, blue laser

Citation: Nersesyan M., Polev G., Popadyuk V., Muntean V.Our First Experience of Using Blue Light Laser for Endoscopic Endonasal Removal of Juvenile Angiofibromas Otorhinolaryngology, Head and Neck Pathology (ORLHNP). 2023; 2 (4): 67-73.

https://doi.org/10.59315/ORLHNP.2023-2-4.67-73

Academic Editor: Valentin Popadyuk

Received: 13.12.2023
Revised: 20.12.2023
Accepted: 01.01.2024
Published: 30.01.2024

1. Introduction

Juvenile nasal angiofibroma (JNA) is a benign vascular neoplasm which affects young males between 9 and 19 years of age and accounts for 0.05% of all head and neck tumors [1]. Glad and colleagues [2] reported an incidence of JA in Denmark of 0.4 cases per million inhabitants per year. In the Middle East and India, the incidence seems to be much higher than in Europe [3].

Surgical removal of JNA is method of choice of its treatment [4, 5] and is considered as one of the most difficult surgeries in otorhinolaryngology because it is very often associated with profuse, streaming bleeding. Massive blood loss in advanced cases can be of 1 or 2 amounts of blood volume circulation, and often may need blood transfusion. Therefore it is actually to develop new methods of reducing operative blood loss. Laser methods of surgical treatment have been actively used in otorhinolaryngology in past years because of apparition of new lasers with advanced properties. The short-wave blue laser with a wavelength of 445 nm, is used in Europe in oto- and laryngosurgery, but was not used in rhinology [28]. The database is limited yet, but we suppose that it may have some potential advantages in rhinosurgery, and particularly in removal of JNA.

The purpose of this paper is to review the literature and to describe our first experience of using a new blue laser in juvenile angiofibroma surgery.

2. Patients and Methods

We treated surgical 7 patients with JNA stage 3-4 according to Snyderman classification and used blue laser at some stages of the intervention. All patients were male, 10-17 years old, mean age 13.8 years. All patients underwent superselective angiography and vascular embolization of juvenile angiofibroma preoperatively, followed by endoscopic endonasal tumor removal. Two of the patients were admitted with continued angiofibroma growth after surgical treatment with embolization in another hospital, while the remaining patients was primary diagnosed.

During surgery we used mono- and bipolar coagulators, vessel clipping and surgicelle hemostatic sponge. In addition, we used the WOLF TruBlue blue laser with a tissue penetration depth of 445 nm. TruBlue is the smallest laser system for coagulation, vaporization and bloodless surgery, combined in an extremely flexible fiber. It is a diode laser, with a penetration depth of 0.1 mm. TruBlue combines the advantages of the CO2 laser with those of the KTP laser [6].

3. Results

The average blood loss during surgery was 150 (50; 350) ml; there were no surgical complications. There were minimal reactive changes in the nose. All patients were discharged on the 2nd or 3rd day after the surgery.

The particularity of laser exposure was the possibility of coagulation and tissue cutting even in conditions of heavy bleeding (fig. 1) and minimal burns of the surrounding tissues after laser exposure(fig. 2, fig. 3, fig. 4)

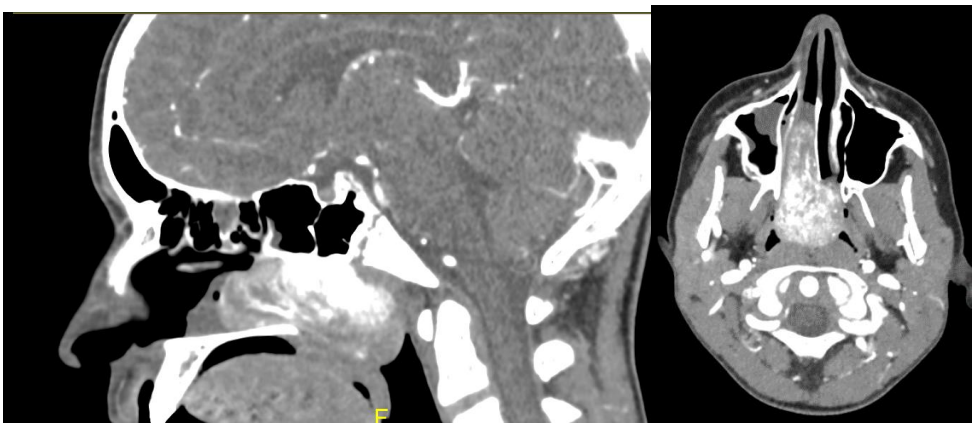

Figure 1. CT image of a patient with angiofibroma

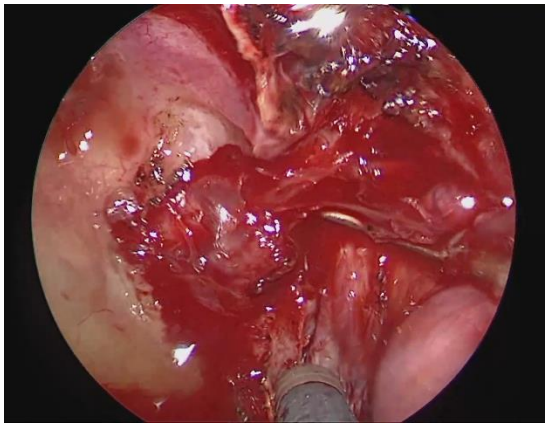

Figure 2. Endoscopic view during the surgery: posterior wall of the maxillary sinus had removed, JNA, in pterigopalatine fossa (shown in white arrow), the place of its origine was removed.

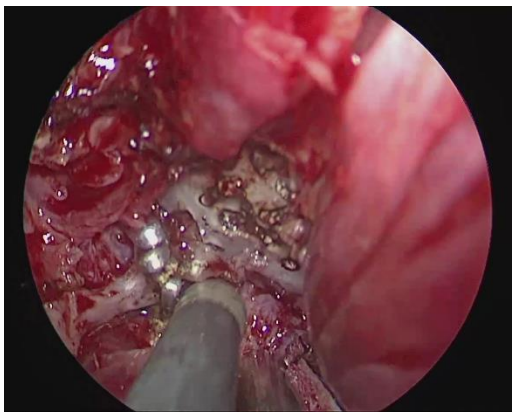

Figure 3. The same endoscopic view after endooscopic displacement of JNA down into nasopharynx. The maxillary artery was clipped. The place of blue laser exposure (shown in white arrow). There is seen no bleeding, minimal trauma of mucosa.

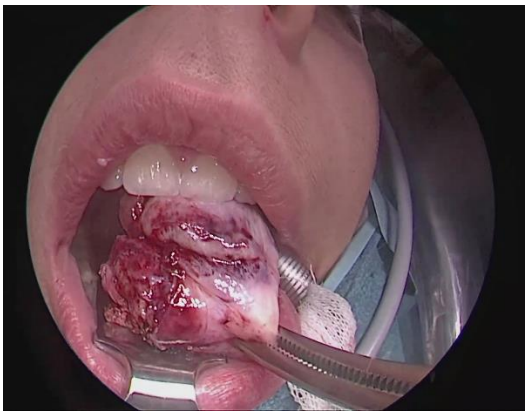

Figure 4. The step of transoral removal of juvenile angiofibroma. There is no bleeding, and minmal trauma without submucosal necrosis of big stage 3 JA by Karl Snyderman classification.

4. Discussion

JNA is a rare lesion, which affects male adolescents and frequently regresses only after full development of secondary sex characteristics. This fact provided the evidence of hormonal influence on JNA growth [7]. Hormonal pathogenesis of this lesion is still a matter of debate, in spite of several reports of presence of androgen and / or estrogen receptors and their role in the tumor development or regression [8-10].

Although several nonsurgical methods have been proposed, surgery is unanimously considered the treatment of choice for JNA. In the last two decades, the surgical approach to the lesion has considerably evolved mainly in relation to the indication of endoscopic techniques. Transpalatal, transpharyngeal, transfacial through lateral rhinotomy, midfacial degloving, and Le Fort I osteotomy, other than infratemporal and subtemporal lateral approaches [11, 12, 13] were once the traditional surgical methods commonly performed to remove JNA. Advances in radiological imaging and improvements of embolization techniques have significantly contributed to better preoperative management and treatment planning. Moreover, increasing experience in endoscopic surgery together with better understanding sinonasal anatomy, provide the possibility to create approach through the nose such to the orbit, infratemporal fossa, masticatory space, parasellar region, furthermore the using intraoperative navigation, and the well-known morbidity associated with external procedures have made an endoscopic approach as preferable in JNA management. Due to the fact that one of the most challenging aspects in JNA surgery is control of intraoperative bleeding, the cooperation anesthesiologists with endoscopic skull base surgeons, the using blood saving methods, in particularly cell saver [14], and hemostatic materials help the surgeon to control bleeding [15].

The first surgical step to create endoscopic approach is to expose JNA as extensively as possible by middle turbinectomy, ethmoidectomy, wide antrostomy and sphenoidotomy [16]. Resection of the posterior third of the nasal septum can also enhances the exposure of the nasopharyngeal portion of the lesion. The posterior wall of the maxillary sinus has to be resected laterally as much as lateral as the lesion spreading into the pterygopalatine and/or infratemporal fossae. For JNA which involving far into infratemporal fossa, lateral exposure through a so-called Sturmann-Canfield maxillectomy can be used. All these provides possibility to make a resection of the le-

sion from anteromedial corner of the maxillary sinus [17]. An endoscopically assisted antral window approach through the anterior wall of the maxillary sinus, as proposed by Pasquini et al. [18], may be considered a possible alternative. Another important principle in the resection of large-volume lesions is the fragmentation technique ("piece-meal" resection) that helps to completely assess the extension without an increased risk of recurrence [19]. During dissection, to maintain a proper cleavage plain between the tumor and adjacent tissues, a four-handed technique is highly recommended [20]. The procedure is completed by accurate subperiosteal dissection of the tumor attachment and subsequent extensive drilling of the basisphenoid and other bone area where the JA is adhered to remove residual disease, which may not be immediately evident, and prevent its regrowth [21].

Because of its high degree of vascularization, bleeding during surgery is a crucial topic. Some studies compared the blood loss between endoscopic and external approaches, showing a lower loss in endoscopic surgery [21, 22]. However, the reliability of these data requires confirmation since JNA treated by an open approach usually have a higher stage than those resected endoscopically. Another question widely discussed in literature is the reduction of intraoperative bleeding, thanks to preoperative embolization. Some authors have correlated the amount of blood loss with the quality of embolization and with tumor extension [23, 24]. Glad et al. [25] showed a statistically significant decrease in bleeding between the nonembolized (650 mL) and the embolized group (1200 mL).

To better control bleeding during the procedure, several authors have proposed the use of diode laser, KTP laser, or ultrasonic scalpel [20; 27].

Although surgical lasers were introduced more than 30 years ago, their use and popularity in nasal and sinus disease have been limited. Even so, there are many practitioners who find the laser a valuable surgical tool for nasal and sinus disease, either alone or in combination with other treatment modalities. The range of surgical interventions in ENT practice covers both tissues with abundant blood supply, where the hemostatic properties of the laser should be fully realized, and areas requiring the most delicate approach, where any excessive thermal damage may lead to scarring (vocal folds) [29]. Laser sinus surgery is limited by the inability of most lasers to ablate bone [30]. The common types of lasers that used in the subspecialty of rhinology include argon (Ar), potassium titanyl phosphate (KTP), diode, neodymium-doped yttrium aluminum garnet (Nd: YAG), holmium-doped yttrium aluminum garnet (Ho: YAG), and the most popular carbon dioxide (CO2). Each laser type has different properties for cutting, coagulation, and evaporating of tissues [31]. The ideal laser for rhinology needs to efficiently ablate dense bone, remove soft tissue, and coagulate a dense vascular bed.

The average amount of blood loss during the surgery of advanced stages of JNA is usually 1500-2000 ml. The blood loss in described cases was about 150 ml. There were complications occurred.

The blue light laser combines the photoangiolytic properties of KTP and cutting properties of CO2 lasers. It is equipped with a more flexible, versatile energy conductor - a standard fiber light guide with a diameter of 0.3 to 0.6 mm. Impulse and constant exposure modes could be used [3].

A feature of the laser effect was the minimal burn of the surrounding tissues, the possibility of coagulation and tissue cutting even in conditions of heavy bleeding. This characteristic made the blue laser made it suitable in treatment of hereditary hemorrhagic telangiectasia (HHT) that is accompanied with recurrent nasal bleeding. Very precise coagulation of the vessels without affecting the surrounding tissue and superficial penetration into the tissue has great advantages for patients with HHT, the impact of which can lead to complications in the long term [32].

There is a potential shorter period or recovery after using blue laser because in one experimental study, where an in vitro cell culture model was created to evaluate the effects of a 445 nm diode laser compared to an infrared (IR) diode laser. The blue laser system showed faster wound healing compared to the IR laser [28].

During the surgery we used the Wolf TruBlue Blue Laser at a number of steps, which made it possible to control bleeding from the branches of the sphenopalatine, posterior ethmoidal and septal arteries well.

Intranasal laser surgery, despite the fact that interventions are performed almost bloodlessly, and often do not require nasal packing, indications for its usage are limited, due to deep burning of the nasal mucosa, and alteration of mucociliary clearance therefore lasers are not so often used in rhinology

These surgeries should be done in big specialized centers with all necessary equipment and professional team. Nevertheless, there is no consensus in the literature about its expediently using because of complications, which may occur. It is very important meticulous hemostasis during endoscopic removal juvenile angiofibroma because of deep localization of the tumor and to been able to do surgery in a narrow hole under endoscopic control for to put endoscope closure to the operative field and injured vessels to avoid severe complications.

5. Conclusions

There was first experience of usages of TrueBlue laser during endoscopic endonasal surgery in the world and the first experience of its use during endoscopic removal of the tumor. It is less traumatic and with good possibility to control intraoperative bleeding with very good with wound healing.

TrueBlue laser is good devise in experienced hands. The indications, contraindications were discussed. Further investigations of usage TrueBlue laser should be done. Evaluation of advantages and disadvantages, determination of indications and limits of its use in rhinosurgery.

Application of artificial intelligence:

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

Acknowledgments. Acknowledgement to our Team of Head and Neck Center of Ilyinskaya Clinic and Charitable foundation “Krasivyie deti v krasivom mire”

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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