

Comprehensive Assessment of the Effectiveness and Safety of Conservative Therapy for Chronic Rhinosinusitis

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RESUME The choice of optimal treatment tactics for polypous rhinosinusitis (PRS) still remains a relevant area in modern rhinology.

Purpose of the study. Development of an integrated treatment and diagnostic approach to improve monitoring of the effectiveness and safety of the use of systemic corticosteroids in the treatment of PRS.

Material and methods. 245 patients with PRS were examined and treated. The course of treatment included 14 days of methylprednisolone in combination with long-term administration of intranasal mometasone furoate, irrigation therapy and proton pump blockers. Of these, 57 patients with latent polyposis-purulent rhinosinusitis received an additional short course of systemic antibacterial therapy.

Efficiency treatment was assessed subjectively by the patient during a questionnaire and objectively based on the results of an endoscopic examination of the nasal cavity, computed tomography (CT) of the paranasal sinuses and data from anterior active rhinomanometry (APRM). To assess the safety of systemic corticosteroid therapy, electrochemiluminescence immunoassay for changes in cortisol concentrations in blood serum and its free fraction in saliva was used.

Results. In 168 (68.6%) patients, relief of the main nasal symptoms was found after a course of treatment. Restoration of nasal breathing according to the results of PARM was observed in 68 (27.8%) patients, positive dynamics according to CT data - in 227 (92.7%). Relapses of the polyposis process were not observed within 1.5 years in 108 (57.2%) patients with PRS and in 28 (49.7%) patients with polyposis-purulent form of rhinosinusitis. A statistically significant decrease in cortisol secretion in the blood by 283.4 nmol/l and in saliva by 15.2 nmol/l was recorded in the middle of the course of treatment with methylprednisolone ($p < 0.05$).

Conclusion. A combined regimen of corticosteroid therapy for PRS is an effective and safe treatment when dynamically monitoring changes in the concentrations of free and bound forms of cortisol in saliva and blood.

Key words: polyps, rhinosinusitis, corticosteroids, cortisol, nasal obstruction, hormone concentration.

Introduction Over the past 10 years, there has been an increase in the incidence of chronic rhinosinusitis among the population [1]. In the structure of this pathology, chronic polypous rhinosinusitis (PPS) occupies a special position. The long course of the pathological process in the nasal cavity and paranasal sinuses, the high incidence of subclinical forms of the disease, and the recurrent growth of polyps contribute to the development of chronic hypoxia, pathology of the cardiovascular system, and a significant decrease in the quality of life of patients [2–7]. According to a number of observations, PRS occurs in all age groups. Every year, about 20 million patients seek medical help due to the onset or exacerbation of PRS [8]. Particularly severe PRS is observed in patients with various congenital or acquired pathologies of the bronchopulmonary system, as well as allergic reactions. The addition of infectious agents to the above group of patients contributes to the development of widespread

damage to the upper and lower respiratory tract, which creates significant difficulties in choosing the optimal tactics for patient management [8-11]. Today, corticosteroids are the main drugs for the treatment of PRS, since they allow them to influence almost all known links in the pathogenesis of PRS [12, 13]. In this case, preference is usually given to intranasal corticosteroids [8, 12, 14]. Systemic corticosteroid therapy (SCT) is used in the treatment of PRS to a limited extent in the form of monotherapy or as part of combination regimens for severe and uncontrolled polyposis and bronchial asthma [3, 6, 8, 14]. The limited prescription of corticosteroids is primarily due to the risk of developing a wide range of side effects [15, 16]. In this regard, the validity of the use of SCT in patients with PRS should be considered from two points of view: an objective substantiation of the effectiveness of treatment in relation to standard approaches and the implementation of reliable control over the safety of its implementation [8, 14, 16]. However, in routine practice, as a rule, an objective functional assessment of nasal breathing is not performed, and diagnosis is based on an analysis of changes in the main symptoms of the disease, the degree of spread of the polypous process in the nasal cavity and paranasal sinuses according to the results of computed tomography and endoscopy, which creates an incomplete picture of the condition sick. It should also be noted that the causes of "steroidophobia" are the lack of a unified diagnostic algorithm for monitoring the safety of taking systemic corticosteroids [4, 8, 14-16]. Thus, to increase the effectiveness of treatment of PRS and implement strict control over the safety of the therapy, it is important to develop comprehensive treatment and diagnostic approaches. The purpose of the study was to develop a comprehensive treatment and diagnostic approach to improve monitoring of the effectiveness and safety of the use of systemic corticosteroids in the treatment of PRS and polyposis-purulent rhinosinusitis (PPRS).

Material and methods On the basis of the Federal State Budgetary Institution "St. Petersburg Research Institute of Ear, Throat, Nose and Speech" of the Ministry of Health of the Russian Federation, in the period from 2012 to 2017, 245 patients with PRS were examined. Inclusion criteria for the study: age over 18 years, presence of bilateral polyposis in the nasal cavity and/or paranasal sinuses, absence of intolerance to corticosteroids, pregnancy, exacerbation of the purulent process, established mental disorders, drug addiction, cystic fibrosis, contraindications to the administration of systemic steroids, and no history of taking systemic corticosteroids in the last 3 months. The patients were divided into two groups. Group 1 included 188 (100%) patients with PRS without signs of purulent inflammation, who were prescribed a combined regimen of corticosteroid therapy: subgroup 1a - 125 (66.5%) patients without concomitant pathology of the bronchopulmonary system; subgroup 1b - 63 (33.5%) patients with bronchial asthma. Group 2 included 57 (100%) patients with PHRS without exacerbation of the inflammatory process, who, in addition to the combined regimen of corticosteroid therapy, were additionally prescribed a short course of systemic antibacterial therapy: subgroup 2a - 30 (52.6%) patients without concomitant pathology of the bronchopulmonary system; subgroup 2b - 27 (47.8%) patients with concomitant bronchial asthma. The examination program before the start of treatment included: collection of complaints and clarification of medical history, general otorhinolaryngological examination. The main symptoms of the disease were identified using a questionnaire; the severity of the latter was assessed using a developed scale from 0 to 4 points: 0 points - absence of symptoms; 1 point - mild symptoms; 2 points - moderately severe symptoms; 3 points - severe symptoms; 4 points - significantly pronounced symptoms. Instrumental examination methods included: endoscopic examination of the nasal cavity with a rigid endoscope of the Hopkins system with an optical angle of 0° and 30°, multislice computed tomography (MSCT) of the paranasal sinuses on a SOMATOM Emotion 16 tomograph, followed by reconstruction of the obtained images in the Radiant program. The degree of prevalence of the polypous process in the nasal cavity and paranasal sinuses was assessed according to the classification of G.Z. Piskunova and S.Z. Piskunova (2002). An objective assessment of the respiratory function of the nose was performed in all patients who did not have perforation of the nasal septum and complete obstruction of one or both nasal passages by polyps using the RHINO-SYS complex based on the analysis of anterior active rhinomanometry (APRM) indicators:

total nasal resistance (cPa/ml in the SI system) and the velocity of the total nasal flow (ml/s in the SI system), the degree of nasal obstruction was established in accordance with the recommendations of the International Standardization Committee on the Objective Assessment of the Nasal Airway [17]. At the same time, an objective assessment of nasal breathing function in connection with the above criteria was performed in 201 patients (158 patients in group 1 and 43 in group 2). Electrochemiluminescent immunoassay ECLIA changes in the concentration of the bound form of cortisol in the blood serum and the free fraction of the hormone in saliva was performed in all patients to monitor the state of the hypothalamic-pituitary-adrenal system while taking a systemic corticosteroid. The collection of materials was carried out taking into account the peaks of physiological cortisol secretion from 8.00 to 10.00 in the morning according to the developed method [18]. After implementing a comprehensive examination plan, patients in group 1 were given a course of conservative treatment, including simultaneous administration of the following medications: 1) methylprednisolone - orally for 14 days, starting at 40 mg/day with a gradual reduction in the dosage of the drug to a maintenance dose of 4 mg/day; 2) mometasone furoate in the form of a nasal spray, 400 mcg/day in each half of the nose for 6 months; 3) omeprazole 1 capsule (20 mg) 2 times a day for 16 days to prevent the ulcerogenic effect of methylprednisolone in all patients; 4) irrigation therapy with isotonic saline solutions of the nasal cavity - 2-3 times a day for 6 months. The diet included a low-calorie diet, rich in protein, potassium, calcium and low in sodium. Patients of group 2, starting from the 8th day of taking methylprednisolone, were additionally prescribed amoxicillin clavulanate 875±125 mg 2 times a day for 7 days to prevent exacerbation of the purulent process in the early stages after discontinuation of systemic corticosteroid therapy. The effectiveness of the combined corticosteroid therapy regimen was assessed subjectively based on an analysis of changes in the main clinical symptoms according to questionnaire data, according to a developed scale from 0 to 4 points, on the 8th, 16th days of treatment, 1 and 3 months from the start of treatment, after 6 months and 1 year after the appointment of SCT. Objectively, the results of the treatment were analyzed according to the data of anterior rhinoscopy, endoscopy of the nasal cavity, MSCT of the paranasal sinuses and indicators of anterior active rhinomanometry after the course of treatment 6 months after treatment. The safety of the combined regimen of systemic corticosteroid therapy in relation to the effects on the hypothalamic-pituitary-adrenal system was recorded through dynamic monitoring of cortisol concentrations in the blood and saliva according to the developed method, taking into account the peaks of physiological secretion from 8.00 to 10.00 in the morning on the 8th, 16th day of treatment and after 1, 3, and 6 months from the start of treatment [18]. Analytical and statistical components of the work, construction of tables and graphs were carried out using licensed software Statistica for Windows, V. 5.5, Microsoft Word 2010 and Microsoft Excel 2010. The significance of certain changes in one sample or differences in results for different samples was assessed by T-Student's criterion. To estimate the limits of the scatter of parameters, we used an estimate of the confidence interval (CI) of the distribution according to which this parameter was distributed under the present assumption. Results and discussion Among the patients of group 1 there were 109 men, 79 women; the average age of the patients was 46.12±13.99 years. Group 2 included 32 men and 25 women; the average age of the patients was 42.94±13.93 years. The established age characteristics emphasized the predominant distribution of PRS and PHRS among the working population, which has important social and economic significance. The differences in the mean ages of men and women between groups were not statistically significant ($p \geq 0.05$). During the course of treatment, both groups showed pronounced positive dynamics in terms of reducing the main clinical symptoms. In group 1, already on the 8th day of treatment, 166 (88.3%) patients showed a significant decrease in the severity of nasal symptoms (1.3 ± 0.4 points). Among patients in group 2, relief of the main clinical symptoms occurred somewhat more slowly. A significant decrease in nasal symptoms (2.1 ± 0.2 points versus 3.4 ± 0.5 points) was recorded in this case only 16 days after the start of treatment in 49 (86.0%) patients. It should be noted that in 7 (53.8%) patients of the 1st group and in 6 (60.0%) patients of the 2nd group with an

objective severe degree of nasal breathing disturbance that persisted after treatment, a noticeable improvement in nasal breathing was subjectively noted, which indicates on patients' underestimation of nasal breathing disorders due to the gradual and long-term course of the polyposis process. The positive impact of the developed course of conservative therapy was noted in relation to the stabilization and control of the course of bronchial asthma in 54 (85.7%) patients of subgroup 1b and in 22 (81.48%) from subgroup 2b. Comparison of the relative number of relapses of the polyposis process after A single course of treatment in study groups registered after 3 and 6 months, 1 and 1.5 years showed the development of the most frequent relapses of the polyposis process in patients with PHRS. The absence of relapses within 1.5 years was detected in 108 (57.2%) patients of group 1 versus 28 (49.7%) patients of group 2. Repeated courses of treatment every 1-1.5 years made it possible to maintain stable remission in 132 (70.2%) patients of the 1st group and in 26 (45.6%) patients of the 2nd group. The period of observation of patients ranged from 3 months to 6 years, the average period of observation was 3.9 years. Determination of cortisol content in the blood and saliva (bound and free forms) in patients of groups 1 and 2 before taking systemic corticosteroids did not reveal statistically significant differences between the groups and in relation to the physiological parameters of the hormone ($p \geq 0.05$). There were also no statistically significant differences in cortisol levels between subgroups differing in the presence or absence of bronchopulmonary pathology ($p \geq 0.05$). Registration of cortisol concentration on the 8th day of SCT showed a statistically significant decrease in the secretion of this hormone by 283.4 nmol/l. Stage I of polypous lesions of the nasal cavity and paranasal sinuses - in 11 (19.3%) patients, stage II was determined in 25 (43.9%) patients, stage III - in 3 (5.3%) patients. The absence of dynamics according to MSCT data of the paranasal sinuses was noted in 3 (5.3%) patients. According to the results of PARM, in both study groups there was an increase in the number of patients with objective improvement in nasal respiratory function. At the same time, among the subjects of group 1, there was an increase in the number of patients (by 34.3%) with no nasal breathing obstruction, a reduction (by 11.4%) in the number of patients with a moderate degree of obstruction, and a significant decrease (by 55.8%) the number of patients with a pronounced degree of nasal breathing impairment. In group 2, there was a greater increase in the number of patients (by 27.9%) with a mild degree of nasal obstruction and a decrease (by 37.2%) in the prevalence of severe nasal breathing impairment among patients (see Table 1, figure) . It should be noted that in 7 (53.8%) patients of the 1st group and in 6 (60.0%) patients of the 2nd group with an objective severe degree of nasal breathing disturbance that persisted after treatment, a noticeable improvement in nasal breathing was subjectively noted, which indicates on patients' underestimation of nasal breathing disorders due to the gradual and long-term course of the polyposis process. The positive impact of the developed course of conservative therapy was noted in relation to the stabilization and control of the course of bronchial asthma in 54 (85.7%) patients of subgroup 1b and in 22 (81.48%) from subgroup 2b. Comparison of the relative number of relapses of the polyposis process after A single course of treatment in study groups registered after 3 and 6 months, 1 and 1.5 years showed the development of the most frequent relapses of the polyposis process in patients with PHRS. The absence of relapses within 1.5 years was detected in 108 (57.2%) patients of group 1 versus 28 (49.7%) patients of group 2. Repeated courses of treatment every 1-1.5 years made it possible to maintain stable remission in 132 (70.2%) patients of the 1st group and in 26 (45.6%) patients of the 2nd group. The period of observation of patients ranged from 3 months to 6 years, the average period of observation was 3.9 years. Determination of cortisol content in the blood and saliva (bound and free forms) in patients of groups 1 and 2 before taking systemic corticosteroids did not reveal statistically significant differences between the groups and in relation to the physiological parameters of the hormone ($p \geq 0.05$). There were also no statistically significant differences in cortisol levels between subgroups differing in the presence or absence of bronchopulmonary pathology ($p \geq 0.05$). Registration of cortisol concentration on the 8th day of SCT showed a statistically significant decrease in the secretion of this hormone by 283.4 nmol/l. The absence of dynamics according to MSCT data of the paranasal sinuses was noted in 3 (5.3%) patients.

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