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A Study of the Intranasal Glucocorticosteroid Nasonex in the Complex Treatment of Polyposis Rhinosinusitis

Conflict of interest: nothing to declare.
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Abstract

Introduction. Polyposis rhinosinusitis (PRS) is based on a chronic inflammatory hyperplastic process in the mucosa of the nasal cavity and paranasal sinuses (PNS). According to the consensus on biological therapy for PRS in combination with or without bronchial asthma (BA), which is one of the most recent consensus documents of the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA), published in December 2019, the conventional sign of decompensation of medication control is the need for surgical treatment or systemic administration of glucocorticosteroids (GCs) due to active polyp growth. Currently, the basic treatment of patients with PPC is the long-term use of intranasal corticosteroids (INCs), which leads to improved quality of life while minimizing the risk of exacerbations and complications.
Purpose. To evaluate the efficacy of the basic therapy of intranasal glucocorticosteroid nasonex in the complex treatment of polyposis rhinosinusitis in its different phenotypes.
Materials and methods. All patients with recurrent PRS were divided into 3 equal phenotypic groups of 40 people each: group 1 – PRS without bronchial asthma and respiratory allergy, group 2 – PRS and atopy, group 3 – PRS and nonallergic bronchial asthma. The follow-up period was 3 years.
Results. The use of the algorithm of staged therapy of PRS, dynamic observation of these patients by an otorhinolaryngologist and an allergist-immunologist, basic therapy with constant correction of treatment once in 3 months allowed to achieve stabilization of the inflammatory process along the whole length of the respiratory tract and to reduce the need for surgical treatment.
Conclusion. In polyposis rhinosinusitis long-term use of INCs mometasone furoate is the main means of basic antirecurrent therapy and is accompanied by clinical efficacy and absence of undesirable side effects.
Keywords: polyposis rhinosinusitis, therapy, intranasal glucocorticosteroids, cytokines, nasonex

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Исследование интраназального глюкокортикостероида назонекс в комплексном лечении полипозного риносинусита

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Резюме

Введение. В основе полипозного риносинусита (ПРС) лежит хронический воспалительный гиперпластический процесс в слизистой оболочке полости носа и околоносовых пазух (ОНП). По данным консенсуса по биологической терапии ПРС в сочетании с бронхиальной астмой (БА) или без нее, являющегося одним из последних согласительных документов Европейского форума по исследованиям и образованию в области аллергии и заболеваний дыхательных путей (European Forum for Research and Education in Allergy and Airway Diseases, EUFOREA), который был опубликован в декабре 2019 г., условным знаком декомпенсации медикаментозного контроля служит необходимость проведения хирургического лечения или системного введения глюкокортикостероидов (ГКС) из-за активного роста полипов. В настоящий момент базовым лечением пациентов с ПРС является длительное использование интраназальных кортикостероидов (инГКС), что приводит к улучшению качества жизни, сводя к минимуму риск обострений и осложнений.
Цель. Оценить эффективность базовой терапии интраназального глюкокортикостероида назонекс в комплексном лечении полипозного риносинусита при его разных фенотипах.
Материалы и методы. Все пациенты с рецидивирующим ПРС были разделены на 3 равные фенотипические группы по 40 человек в каждой: 1-я группа – ПРС без БА и респираторной аллергии, 2-я группа – ПРС и атопия, 3-я группа – ПРС и неаллергическая БА. Срок наблюдения – 3 года.
Результаты. Использование алгоритма ступенчатой терапии ПРС, динамическое наблюдение этих пациентов оториноларингологом и аллергологом-иммунологом, базовая терапия инГКС с постоянной коррекцией лечения 1 раз в 3 месяца позволило добиться стабилизации воспалительного процесса на всем протяжении дыхательного тракта и снизить потребность в хирургическом лечении.
Заключение. При полипозном риносинусите длительное использование инГКС мометазона фуроата является основным методом базовой противорецидивной терапии и сопровождается клинической эффективностью и отсутствием нежелательных побочных явлений.

Ключевые слова: полипозный риносинусит, терапия, интраназальные глюкокортикостероиды, цитокины, назонекс

■ INTRODUCTION

Polyposis rhinosinusitis (PRS) is based on a chronic inflammatory hyperplastic process in the mucosa of the nasal cavity and paranasal sinuses (PNS). Although many theories of the etiopathogenesis of ORS have been proposed, none of them has been able to reliably explain the process of polyp formation. Mucosal edema is considered to be the structural basis for the development of PRS, with inflammatory mediators, cytokines, and adhesion molecules playing a key role [1]. PRS in most cases shares with bronchial asthma (BA) the pathophysiologic mechanism of Th2-type inflammation with predominance of eosinophils and release of interleukins IL-4, IL-5, IL-13 [2]. The cornerstone of the management of patients with both PRS and BA is the continuous local application of glucocorticosteroids (GCs) with nonspecific anti-inflammatory effect in order to achieve optimal disease control. In case of ineffectiveness of this group of drugs, short courses of systemic administration of GCS or surgical treatment are performed in PRS [3]. The main goal of therapy in the management of patients with PRS is the drug control of the disease, which means increasing the interval of recurrence of polyp tissue growth on the background of minimal baseline conservative therapy. According to the consensus on biologic therapy of PRS with or without BA, which is one of the latest consensus documents of the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA), published in December 2019, the conventional signs of decompensation of drug control are the need for surgical treatment or systemic administration of GCs due to active polyp growth [4]. At the same time in PRS, there is a term "severity of disease", which means the degree of severity of symptoms of the chronic inflammatory process. The patient's persistent presence of nasal congestion, mucopurulent nasal discharge, postnasal syndrome, facial or headache, impaired sense of smell, fatigue, and sleep disturbance for 3 months is considered relevant.

According to this consensus [4], in case of negative dynamics on the background of baseline therapy, there are currently 5 criteria for making a decision on biological anticytokine therapy: 1) proven type 2 inflammatory process based on the determination of a number of biomarkers; 2) the need for systemic therapy with GCs in the last 2 years; 3) significant deterioration of the quality of life; 4) significant impairment of the sense of smell; 5) the presence of comorbid BA. With previous PNS surgery, 3 criteria are sufficient for bilateral PRS. Patients who have never had sinus surgery must meet at least four of the above criteria to be eligible for biologic treatment.

Contraindications to biologic therapy are unilateral process, absence of signs of type 2 inflammation, cystic fibrosis, mucocele, confirmed immunodeficiency state and patient's personal qualities in the form of non-adherence to the prescribed therapy. It is also worth noting that there is considerable variability in the degree of response to biologic therapy due to the current lack of valid diagnostic markers and clinical experience with this group of drugs in PRS. The criteria for a positive response to this type of treatment are:

1) reduction in the size of nasal polyps;
2) decreased need for systemic corticosteroids;

3) dependence of the course of PRS on comorbid conditions;
4) improved quality of life;
5) improved sense of smell.

If 2 criteria are present, the response to treatment is poor; if 3–4 criteria are present, the response is good; if all 5 criteria are present, the response is considered excellent. The first evaluation is carried out 16 weeks after the start of treatment. If there is no effect, the course of anticytokine therapy is discontinued. A repeat evaluation is performed after 1 year.

Therefore, the basic treatment of patients with PRS is the long-term use of intranasal corticosteroids (INGCs), which leads to improved quality of life, while minimizing the risk of exacerbations and complications [5]. They have high topical activity and, due to their rapid inactivation in the liver and low bioavailability, minimal systemic effects [6]. Among this group of drugs, nasonex deserves special attention because the side chain of the furoate ester makes the molecules of this drug very lipophilic, which allows them to be easily absorbed by epitheliocytes and phospholipids of cell membranes of nasal and PNS mucous membranes. This minimizes their systemic action and increases the duration of local effect [7]. The anti-inflammatory effect of mometasone furoate is associated with inhibition of synthesis of Il-1, Il-3, Il-4, Il-5, Il-6, Il-13, tumor necrosis factor (TNF)-α, granulocyte macrophage colony-stimulating factor (GM-CSF, granulocyte macrophage colony-stimulating factor), nitric oxide synthetase, cell adhesion molecules E-selectin and ICAM-1 (intercellular adhesion molecule), inhibition of mucosal remodeling process and activity of the main cells – eosinophils – participants of the pathological process in PRS [8]. Receptors to GCs on the mucous membrane of the nose and paranasal sinuses exist in 4 isoforms, the only active of which is GCRα, the rest GCRβ, GCRδ and GCRγ retain only some features of the full spectrum of activity. The most common of them is GCRβ, which has the ability to bind directly to the active monomer of GCRα, creating an inactive heterodimer, inhibiting the activity of GCRα, which causes its secondary resistance to INGCs. The cytokines IL-1, IL-2, IL-4, IL-13, and TNF-α actively participating in the inflammatory process in PRS activate alternative splicing mechanisms and increase GCRβ expression. Thus, during prolonged inflammation, the density of GCRβ increases, so sensitivity to INGCs may decrease. It has been demonstrated that the mucosa of patients with PRS who do not use INGCs shows higher expression of GCRβ in polyp tissue compared to intact mucosa [8]. This process may be reversible, and after topical and systemic application of GCs in PRS, a significant increase in GCRα expression compared to their baseline level is observed within 2 weeks. This explains the antirecurrent effect of INGCs when they are used for a long period of time.

■ PURPOSE OF THE STUDY

To evaluate the efficacy of basic therapy with intranasal glucocorticosteroid nasonex in the complex treatment of polyposis rhinosinusitis in its different phenotypes.

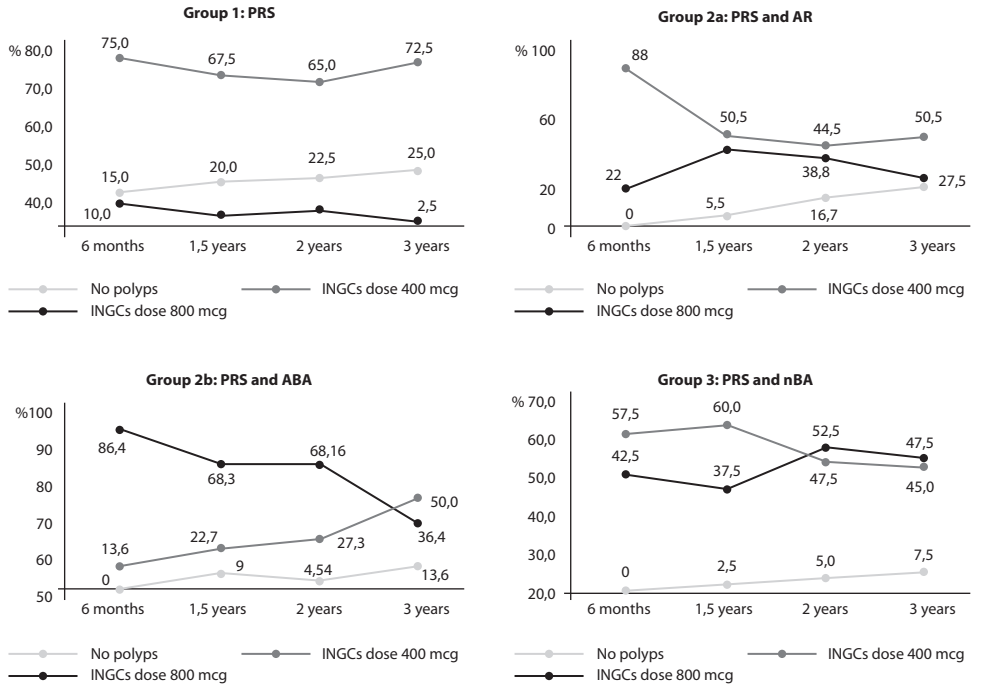
■ MATERIALS AND METHODS

During the period 2019–2023, 120 people (59 males, 61 females) with recurrent PRS permanently residing in Samarkand and Samarkand region, mean age 52.12±11.05 (M±s) were under observation at Samarkand State Medical University. The presence of bilateral polyposis rhinosinusitis was confirmed by endoscopic examination of the nasal cavity and computed tomography of the PNS. All patients were consulted by an

allergologist-immunologist for diagnosis of atopy and BA. Allergological examination included anamnesis collection, scarification skin tests with standardized diagnostic allergens. Exclusion criteria were: unilateral process, presence of BA of any genesis, oncologic, autoimmune pathology, genetic syndromes (cystic fibrosis, allergic granulomatous or eosinophilic angiitis, Charles-Stross syndrome). To confirm or refute the diagnosis of "bronchial asthma", external respiratory function was evaluated, and if necessary, a bronchodilator test was performed (salbutamol at a dose of 100 mcg for up to 4 breaths once). Patients with PRS were divided into 3 equal phenotypic groups: Group 1 included patients with PRS without allergy and bronchial asthma (40 patients, age 51.4±1.3), Group 2 included patients with PRS combined with allergic rhinitis (AR) and/or without allergic BA (ABA) (40 patients, age 51.44±2.28, ABA in 22 patients), Group 3 included patients with PRS combined with non-allergic BA (nBA) (40 patients, age 54, 57±2.7). There were no statistical differences between the groups in terms of the duration of PRS and BA, the prevalence of the pathologic process in the PNS according to CT scan of the PNS, the degree of severity of nasal polyps from the 1st to the 3rd degree [1, 3], and age. Previously, all patients had been operated on for PRS in the scope of functional endoscopic sinus surgery (FESS) with bilateral opening of the lattice, maxillary sinuses, and in some patients – frontal sinuses, after which in 1–3.5 years there was a recurrence of polyp growth, and the patients were referred for repeated surgical treatment. They underwent endoscopic polypotomy from 2 sides in the conditions of a day hospital, after surgical treatment all patients were prescribed Nasonex in the form of spray in the dose of 100 mg in each half of the nose 2 times a day (daily dose 400 mcg) for 6 months as a basic therapy and irrigation therapy of the nasal cavity mucosa [3]. Patients used nasal sprays Nasonex®, Desrinit, and Nosefrin, which contain mometasone furoate and are indicated for the treatment of PRS. A comparative study between the drugs was not conducted, since the efficacy of each of them in this pathology has already been proven. In addition, depending on the PRS phenotype, patients were managed according to the algorithm of stepwise therapy of different PRS phenotypes developed by us [1, 4]. In case of the 2nd and 3rd phenotype, the allergist treated BA and allergic rhinitis at the same time. The first assessment of the nasal cavity was performed 3 months after the surgical intervention; endovideoscopic examination recorded the presence or absence of nasal cavity polyps and the degree of their prevalence. Endoscopic examination of the nasal cavity 6 months after surgery was taken as the starting point of control of the effectiveness of conservative treatment. If no recurrence of polyps was observed, the administration of INGCs was stopped, if aggressive growth of polyps was observed, the daily dose of nasonex was increased up to 800 mcg (based on our own experience in treatment of patients with polyposis rhinosinusitis according to the instructions), if polyposis tissue in the nasal cavity was in the same degree of severity as in 3 months after surgery, patients continued to receive INGCs at a dose of 400 mcg/day. Every 3 months, patients underwent endovideoscopic examination of the nasal cavity and recorded the degree of polyposis process prevalence, which was the only criterion of polyp growth recurrence in our study [1, 3].

■ RESULTS

In the 1st group in PRS without concomitant BA and atopy in 3 months after surgery in 3 people (7.5%) due to active growth of polyps the therapeutic dose of INGCs was increased up to 800 mcg/day, after which the pathological process stabilized (Figure).



Dynamics of the need for the use of different doses of intranasal nasonex in different phenotypes of polyposis rhinosinusitis

After 6 months good result and absence of nasal cavity polyps was observed in 15% of patients, 75% of patients continued using INGCs at the dose of 400 mcg/day, in 4 people (10%) the dose of nasonex was increased up to 800 mcg/day. Complete medication control, allowing withdrawal of baseline therapy with INGCs after 1.5 years, was achieved in 20% of patients, and after 3 years – in 25% of patients in the group.

The absence of polyposis vegetations in the nasal cavity during endoscopic examination and clinical symptoms of chronic inflammatory process of the PNS were noted. In 7 patients (17.5%) FESS was repeatedly performed in the period of 1.5–2.5 years after the beginning of follow-up, and despite the technically correct operation, in 3 months in 2 patients the growth of polyposis tissue resumed. Nevertheless, the main group of patients had a good antirecurrent effect on the background of constant use of INGCs in the dose of 400 mcg/day.

In the 2nd group of patients with atopy in 6 months after the operation all patients had nasal polyps in the nasal cavity at the endoscopic examination, and in 22% – in case of concomitant allergic rhinitis (group 2a) and in 86,4% – in case of comorbid ABA (group 2b) the dose of INGCs was increased up to 800 mcg/day. Two years after the surgical intervention, 16.7% of patients in group 2a and 4.54% in group 2b showed absence of polyposis vegetations in the nasal cavity on the background of drug therapy with INGCs. 44.5% of patients in group 2a and 27.3% in group 2b received standard doses of intranasal

mometasone furoate. During the first 2 years of follow-up uncontrolled course of PRS was observed in 10 patients (25%), 5 patients were reoperated, and all these patients had concomitant ABA in addition to allergic rhinitis. Nevertheless, after 3 years of treatment 22% of patients with concomitant AR and 13.6% of patients with concomitant ABA showed absence of nasal cavity polyps, which allowed to cancel INGCs, in 50% of patients in both groups stabilization of pathological process was achieved against the background of constant use of INGCs in the dose of 400 mcg/day and treatment of concomitant comorbid allergic disease. Thus, concomitant allergic pathology of the upper and lower respiratory tracts led to more complicated drug control of PRS. Group 3 had the most aggressive course of PRS in PRS + nBA. By the end of the second year only 2 people (5%) had an opportunity for discontinuation of the basic therapy with INGCs due to the absence of nasal polyps. During the period of 1–1.5 years after the last operation repeated FESS was performed in 6 people, in 9 more people short courses of systemic corticosteroid therapy were performed. However, by the end of the 3rd year at the next control endoscopic examination of the nasal cavity in 3 people (7.5%) the absence of polyp growth recurrence was noted, and in 45% – medical control was achieved against the background of basic therapy with INGCs at a dose of 400 mcg/day and 47% at a dose of 800 mcg/day with achieved stabilization of the course of nBA.

■ DISCUSSION

Polyposis rhinosinusitis is characterized by persistent inflammation, which requires constant dynamic monitoring and correction of drug treatment depending on the patient's condition. Long-term continuous use of intranasal glucocorticosteroids as a basic therapy allows to reduce the size of polyps and the probability of recurrence after surgery and to reduce the severity of clinical symptoms, including impaired sense of smell and nasal congestion [7]. Management of PRS patients by an otorhinolaryngologist together with an allergist-immunologist allows simultaneous control of the inflammatory process throughout the respiratory tract and joint adjustment of drug treatment regimens. All this allows to control the course of PRS in all clinical phenotypes in patients with recurrent process and reduce the number of surgical interventions. According to our observations, no adverse events were observed in patients using all preparations of mometasone furoate nasal spray, except for occasional burning sensation, despite their long-term use for 3 or more years. A systematic literature review analyzing the effect of modern INGCs on atrophic processes of the nasal mucosa showed that this is a very rare complication in PRS, independent of the drug dose or duration of its use; INGCs had no significant effect on the integrity and did not lead to thinning of epitheliocytes and basal membrane of the mucosa. The decrease in the number of bocaloid cells and submucosal glands after treatment with INGCs in patients with PRS is one of the therapeutic mechanisms leading to a decrease in mucus production and rhinorrhea severity [5], which clinically may be manifested by dryness of the nasal mucosa.

It was noted that there was a great variety of prescribed INGCs, including "off label", which makes no sense due to the increased activity of patients who try to check all prescriptions of doctors in the Internet sources available to them and check the correctness of the prescription of drugs with the instructions [8]. In polyposis rhinosinusitis, the drug containing mometasone furoate is administered in 2 doses (50 mcg) in each half of the nose 2 times a day (total daily dose 400 mcg) to adult patients from 18 years of age [6].

■ CONCLUSION

In polyposis rhinosinusitis, long-term use of nasonex is the main means of basic antirecurrent therapy of this disease and is accompanied by clinical efficacy and absence of serious undesirable side effects.

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