PERIÓDICO TCHÊ QUÍMICA
ARTIGO ORIGINAL

CARACTERÍSTICAS COMPARATIVAS DA SEGURANÇA DOS MÉTODOS DE IMUNOTERAPIA SUBLINGUAL E PARENTERAL

COMPARATIVE CHARACTERISTICS OF SAFETY OF SUBLINGUAL AND PARENTERAL IMMUNOTHERAPY METHODS

СРАВНИТЕЛЬНАЯ ХАРАКТЕРИСТИКА БЕЗОПАСНОСТИ СУБЛИНГВАЛЬНОГО И ПАРЕНТЕРАЛЬНОГО МЕТОДОВ ИММУНОТЕРАПИИ

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RESUMO

Entre um número significativo de alergias, a alergia ao pólen é a mais comum entre crianças e adultos. A alergia ao pólen leva principalmente à irritação do nariz e dos olhos, mas também pode causar dores de cabeça, fraqueza, fadiga e diminuição do tempo de atenção. Uma reação alérgica aguda pode causar o choque anafilático, ou seja, uma queda acentuada da pressão arterial com risco de vida. Essas e muitas outras consequências das reações alérgicas sugerem a necessidade de criar os medicamentos que possam curar uma pessoa alérgica ou interromper a manifestação de reações alergênicas. O objetivo do artigo foi estudar a segurança da imunoterapia específica para alergenos. Os métodos de pesquisa incluem análise da comparação da eficácia de dois métodos de imunoterapia, comparação da segurança dos métodos sublingual e parenteral de administração de vacinas alérgicas e uma avaliação comparativa da segurança dos tipos de imunoterapia específica para alergenos. O estudo envolveu 228 pacientes com severidade variável da febre do feno, entre os quais as crianças de 5 a 18 anos e os adultos (113 pacientes eram homens, 115 eram mulheres). O estudo mostrou que a imunoterapia sublingual aumenta a segurança do tratamento e é um bom substituto para a imunoterapia parenteral, especialmente em crianças. Estudos também confirmaram as evidências científicas bem conhecidas sobre a segurança da imunoterapia sublingual em pacientes com febre do feno. Concluiu-se que a imunoterapia sublingual aumenta a segurança do tratamento e é um bom substituto para o método de imunoterapia parenteral específica para alérgenos, principalmente em pacientes pediátricos, enquanto apresenta várias vantagens, como redução significativa de reações adversas, alta eficiência e conveniência de administração, grande compromisso do paciente e confiança no tratamento, e eliminação da transmissão da infecção.

Palavras-chave: *febre do feno, segurança, imunoterapia sublingual específica para alérgenos, imunoterapia parenteral específica para alérgenos.*

ABSTRACT

Among a significant number of allergies, the most common among children and adults is pollen allergy. Pollen allergies primarily lead to irritation of the nose and eyes, but can also cause headaches, weakness, fatigue, and decreased attention span. In an acute allergic reaction, anaphylactic shock can occur, that is, a life-threatening sharp drop in blood pressure. These and many other consequences of allergic reactions imply the need to create drugs that could cure a person of allergies or stop the manifestation of allergen reactions. The aim of the article was to study the safety of allergen-specific immunotherapy. The research methods included an analysis of the comparison of the effectiveness of two immunotherapy methods, a comparison of the safety of sublingual and parenteral methods of administering allergic vaccines, a comparative assessment of the safety of types of allergen-specific immunotherapy. The study involved 228 patients with varying severity of hay fever, among whom were children from 5 to 18 years old and an adult population (113 patients were men, 115 were women). The study revealed that sublingual immunotherapy increases the safety of treatment and is a good substitute for parenteral immunotherapy, especially in children. The studies have also confirmed well-known

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scientific evidence on the safety of sublingual immunotherapy in patients with hay fever. It was concluded that sublingual immunotherapy increases the safety of treatment and is a good substitute for the parenteral allergen-specific immunotherapy method, especially in pediatric patients, while having several advantages, such as a significant reduction in adverse reactions, high potency, and a convenient mode of administration, greater patient commitment and trust in treatment, and the elimination of infection transmission.

Keywords: *pollinosis, safety, sublingual allergen-specific immunotherapy, parenteral allergen-specific immunotherapy.*

АННОТАЦИЯ

Среди разнообразного числа аллергий наиболее распространенной среди детей и взрослых является аллергия на пыльцу. Аллергия на пыльцу в первую очередь приводит к раздражению носа и глаз, но также может вызывать головные боли, слабость, усталость и снижение концентрации внимания. При острой аллергической реакции может возникнуть анафилактический шок, то есть опасное для жизни резкое падение артериального давления. Эти и многие другие последствия аллергических реакций предполагают необходимость создания лекарств, которые могли бы вылечить человека от аллергии или остановить проявление аллергенных реакций. Целью статьи является изучение безопасности аллерген-специфической иммунотерапии. Методы исследования включают анализ сравнения эффективности двух методов иммунотерапии, сравнение безопасности сублингвальных и парентеральных методов введения аллергических вакцин, сравнительную оценку безопасности типов аллерген-специфической иммунотерапии. В исследовании приняли участие 228 пациентов с различной степенью тяжести сенной лихорадки, среди которых были дети от 5 до 18 лет и взрослое население (113 пациентов были мужчины, 115 – были женщины). Исследование показало, что сублингвальная иммунотерапия повышает безопасность лечения и является хорошей заменой парентеральной иммунотерапии, особенно у детей. Исследования также подтвердили хорошо известные научные данные о безопасности сублингвальной иммунотерапии у пациентов с поллинозом. Были сделан вывод о том, что сублингвальная иммунотерапия повышает безопасность лечения и является хорошей заменой метода парентеральной аллерген-специфической иммунотерапии, особенно у педиатрических пациентов, при этом она обладает рядом преимуществ, таких как значительное снижение побочных реакций, высокая эффективность и удобство способ введения, большая приверженность пациента и доверие к лечению, а также устранение передачи инфекции.

Ключевые слова: *поллиноз, безопасность, сублингвальная аллерген-специфическая иммунотерапия, парентеральная аллерген-специфическая иммунотерапия.*

1. INTRODUCTION:

In the etiological structure of allergic diseases, pollen allergy is one of the leading places. Due to its high prevalence, pollen allergy in children and adults remains one of the significant problems of pediatrics and clinical allergology. Pollinosis significantly reduces the quality of life of patients in the spring-summer period of the year, disrupting its medical and social adaptation. A sharp surge in the incidence over the past two decades is associated with an increase in the allergenic load on humans, which is associated largely with environmental pollution, including atmospheric air, drinking water, food and soil, chemicals that act as allergens, and the current century will be the age of allergies, taking the scale of the medical and social problem (Shvetsova and Korotkova, 2017; Waldron and Kim, 2020).

The incidence of allergies has risen sharply over the past 30 years, especially in developed countries. According to WHO, from 2001 to 2010, the number of allergic people in the world increased by 20%. By 2025, according to WHO, 50% of the world's population will already suffer from this ailment. Now, according to the European Academy of Allergology and Clinical Immunology (EAACI), there are 150 million chronic allergy sufferers in Europe (20% of the population). Growth rates depend on the specific country and the diet of its inhabitants. The spread of allergies is especially noticeable in Western countries. In Britain, between 1995 and 2016, the incidence of allergies increased five-fold. In Kazakhstan, pollinosis is mainly caused by weeds. An allergic reaction to wormwood, quinoa and ragweed is almost 23% of all residents who are allergic to flowering. In the second place – cereals (10.46%), in third – the pollen of trees (11.06%) (Carlson and Coop, 2019).

Allergens can cause very diverse reactions that can seriously affect a person’s life. Some people have a runny nose and sneezing. Others have itchy, unsightly rashes or swelling and trouble breathing (Tosca *et al.,* 2020; Dick *et al.,*

2020; Penagos and Durham, 2019). Sometimes an allergic reaction can be life threatening. Anaphylaxis can occur, which, in the absence of immediate treatment, can be fatal. Today, allergen-specific immunotherapy is the only one alternative method for the treatment of hay fever, recognized by many domestic and foreign allergists. It is known that one of the most important requirements of pharmacotherapy for patients is safety. Sublingual immunotherapy is especially indicated for children, due to its greater safety compared to other approaches of ASIT (Saltabayeva and Morenko, 2015).

2. MATERIALS AND METHODS:

Surveys were carried out on the basis of the National Scientific Center for Motherhood and Childhood, in the medical and health center “Umit” and the Astana City Children's Hospital N1. The study involved 228 patients with varying degrees of severity of hay fever, among whom were children from 5 to 18 years old and an adult population (113 patients were males, 115 were females). The average age was 23.5 ± 0.9 years, the minimum age was 5 years, the maximum was 60 years. The studied respondents were randomized into two groups: group 1 included 126 (55.3%) patients who took sublingual immunotherapy, group 2 included 102 (44.7%) patients who received parenteral immunotherapy.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent Informed consent was obtained from all individual participants included in the study.

The safety of sublingual and parenteral allergen-specific immunotherapy was assessed by the frequency and severity of undesirable local and systemic reactions. In the manufacturer's instructions for use of the drug, the effects are described only in the form of general malaise, drowsiness, fatigue and fever.

3. RESULTS AND DISCUSSION:

Over 3 years of observations, were noted both local and systemic adverse events. Local adverse events (AEs) were presented with PIT in the form of hyperemia, itching and infiltration at the injection site, with SLIT – in the form of edema of the oral mucosa at the site of the allergen, lip swelling, itching in the mouth, sore throat and numbness of the tongue. Hives, bronchial obstruction, rhinoconjunctivitis, nausea, fatigue were attributed to systemic adverse reactions (Saltabayeva *et al.,* 2016b).

When SLIT local adverse events developed, as a rule, within 5-10 minutes after application of the allergen without disrupting the general well-being of the patient. With duration of local AE up to 15-30 minutes, was recommended the continuation of the course without changing the treatment regimen, with repeated relapsed AE repeated the previous dose of the drug of the same concentration. With persistent conservation of local AEs, it was recommended to return to the dose at which there was no development of exacerbations, and to continue the course of treatment starting from this dose. In the absence of the effect of this technique, we prescribed a course of treatment on the background of antihistamines, after passing the “critical concentration” symptomatic drugs were canceled.

Systemic adverse events were stopped by standard methods, then they recommended continuation of the course with a mandatory change in the treatment regimen: the immunotherapy was repeated starting from the administration of the minimum dose of the previous allergen concentration. With the re-development of common AEs, the threshold dose of allergic vaccine, which was later regarded as an individual threshold dose, took an allergen concentration that did not cause the development of common AEs. This dose was “maximal” for the patient, and was administered during the maintenance phase. During the use of sublingual ASIT, most undesirable reactions were resolved mostly on their own, without requiring discontinuation of treatment or correction of the dose regimen.

When conducting 1 course SLIT in 1 group of patients on the background of sublingual ASIT, local adverse events (swelling of the oral mucosa at the site of the allergen, lip swelling, itching in the mouth, sore throat, numbness of the tongue) developed in 35 (27.75%) treated patients with pollinosis (Table 1). All AEs lasted for 5-15 minutes after the application of the allergen and passed on their own within 30 minutes. 18 (14.29%) patients developed general AEs (hives, bronchial obstruction, rhinoconjunctivitis, nausea, fatigue), which were of a mild nature and were stopped within 24 hours without requiring a change in treatment regimen or discontinuation of therapy.

These reactions were described in the instructions for use of the drug and were expected

during the study. In studies of some scholars, when conducting SLIT, local undesirable phenomena, such as swelling of the vocal fold, swelling and burning of the lips, burning of the tongue, swelling of the tongue and the mucous membranes of the mouth, were noted in 15.1% of respondents, general AE cough, nausea, vomiting, heartburn) – in 30% of patients (Haiduk, 2013; Baranov *et al.,* 2002). As a rule, general AEs were light in nature, and did not require the cancellation of therapy. In studies by other authors, local adverse reactions such as burning, itching, tingling, and swelling in the oral cavity were observed in 20% of patients where the reactions were mild, occurred immediately after taking the allergen, and passed on their own within 30 minutes (Goryachkina and Nenasheva, 2008). Systemic reactions in the form of acute urticaria, lung respiratory discomfort were detected in 12.5% of patients. According to other scientists, systemic reactions in the form of coughing, shortness of breath, nasal congestion and local – in the form of itching in the eye area occurred in 14.2 and 5.7% of treated patients, respectively (Revyakina, 2007).

During the 2nd course of SLIT, local reactions in the form of edema of the oral mucosa at the site of allergen, lip swelling, itching in the mouth, sore throat, numbness of the tongue and general, such as rhinoconjunctivitis, fatigue, occurred in 16 (12.7%) and 3 (2.38%) patients, respectively. Total complications during the 2nd course of immunotherapy were recorded in 19 (15.08%) patients. All AEs were lightweight, and did not require the termination of immunotherapy. During the last 3rd course of SLIT, mainly local AEs (itching in the mouth, sore throat) occurred in 9 (7.14%) patients, and in general 2 (1.59%), in the form of rhinoconjunctivitis. Total AEs were observed in 11 (8.73%) patients. During the study, not a single serious adverse event was recorded (Figure 1) (Saltabayeva and Morenko, 2017).

Analysis of adverse events in the group of patients who received parenteral ASIT showed that during the 1st course of immunotherapy, AE was observed in 62 patients (60.78%), systemic reactions – in 26 (25.49%) patients. Of these, 19 patients developed systemic reactions 15–30 minutes after the administration of allergic vaccines and were presented as localized hives, rhinoconjunctivitis, bronchial obstruction with a decrease in EFM to 60%. The development of generalized hives occurred in 3 patients (2.94%), bronchial obstruction in 4 patients (3.92%), rhinoconjunctivitis in 11 (10.78%) people. According to the classification of systemic reactions that occur during injection therapy, these AHs were attributed to the lungs (1 point) and moderate (2 points) systemic reactions (Table 2).

Local adverse reactions were noted in 36 (35.29%), of them in 3 (2.94%) patients in the form of infiltrate more than 30 mm with the introduction of PIT at a dilution of 1:10. These patients required discontinuation of immunotherapy for the period of treatment with a further change in treatment regimen.

Undesirable reactions during the 2nd course were detected in 38 (37.25%) patients. Systemic reactions occurred in 10 (9.80%) patients: generalized urticaria in 1 (0.98%) patient and an attack of bronchial asthma with a decrease in peak expiratory flow rate to 40% in 2 (1.96) patients, rhinoconjunctivitis in 6 (5.88%), fatigue in 1 (0.98%), which were regarded as severe, but not life-threatening (Saltabayeva, 2017).

Local adverse events occurred in 27.45% (28 patients) of cases in the form of itching, swelling, hyperemia at the injection site and infiltration of more than 30 mm at the injection site. The analysis of AE has shown that they developed, as a rule, in violation of the diet (the use of causally significant allergens – honey, halva, nuts). Therapy of systemic reactions was carried out according to recommended standards, after normalization of the patients' condition; the course was continued according to an individual scheme. During the last 3rd course of PIT, local AEs manifested in 10 (9.80%) patients, common – in 3 (2.94%). Total AEs were noted in 13 (12.74%) patients (Figure 2) (Saltabayeva *et al.,* 2016a).

The frequency of local reactions during the 1st and 2nd course PIT was not significantly different. With the development of local reactions, a course of antihistamines was recommended, with continued immunotherapy, the dose of the allergen was repeated, at which the local reaction developed. With the recurrence of a local reaction, they took a break for 2-3 days, followed by a repeat dose of allergic vaccine (Figure 3).

Analysis of the comparison of the effectiveness of the two methods of immunotherapy showed that with sublingual immunotherapy, the dose of the collected allergen is much higher than that of parenteral immunotherapy. Undesirable local and systemic reactions during PIT (60.78%) were manifested 1.5 times more often compared to sublingual (42.07%) type of therapy.

Important for us was the comparison of the safety of sublingual and parenteral methods of

allergic vaccine administration. Local suburbs with sublingual immunotherapy were presented mainly as a local reaction in the oral cavity with duration of no more than 30 minutes and as requiring medical correction. Systemic adverse events in sublingual immunotherapy were attributed to the lungs and did not require discontinuation of immunotherapy and changes in the treatment regimen. During the parenteral type of ASIT, local AEs required correction of the immunotherapy regimen. With the development of systemic reactions with the parenteral administration of an allergen, both light systemic AEs and moderate and severe but not life-threatening reactions took place. This complication of the parenteral ASIT method required the discontinuation of treatment and the development of an individualized treatment regimen, but none of the patients had treatment discontinued (Saltabayeva, 2016a).

In a comparative assessment of studying adverse events in patients with pollinosis of different ages, the following values were obtained, as shown in Figures 4 and 5.

In the study of the safety of ASIT species for a three-year period in the age subgroup from 5 to 18 years showed that against the background of SLIT 41.27%, against the background of PIT 76.60% ($p < 0.001$), in the subgroup from 18 to 45 years on the background of SLIT in 52.17%, on the background of PIT in 67.50% ($p < 0.05$), in the subgroup from 45 to 60 years on the background of SLIT in 58.82%, on the background of PIT in 73.33% of patients local adverse events were reported with pollinosis ($p < 0.001$).

According to the results of observation of patients with pollinosis, systemic adverse reactions in the age period from 5 to 18 years were detected on the background of SLIT in 17.46%, on the background of PIT in 42.55% ($p < 0.01$), in the age subgroup from 18 up to 45 years on the background of SLIT in 19.67%, on the background of PIT at 35.00% ($p < 0.01$), in the age subgroup from 45 to 60 years on the background of SLIT on 17.65%, on the background of PIT on 33.33% of the surveyed respondents ($p < 0.001$).

According to the above data, during the three-year period, it became known that, against the background of parenteral ASIT, local AEs were observed 1.9 times more often in patients aged 5 to 18, systemic AEs 2.4 times 45 years old local AEs 1.3 times, systemic ones 1.8 times; at the age of 45 to 60 years old local AEs are 1.2 times more often and systemic ones 1.9 times more than sublingual allergen-specific immunotherapy ($p < 0.001$; $p < 0.01$; $p < 0.001$).

In the analysis of adverse events, it was found that in patients with pollinosis of all the studied groups, they manifested themselves at high doses of the administered allergens and when the diet was disturbed during the course of immunotherapy, i.e. use of cross food allergens that have common antigens with pollen from pollen.

Our research also confirmed the well-known scientific data on the safety of sublingual immunotherapy in patients with pollinosis. In this multicenter, randomized, placebo-controlled study, this high safety was indicated by Durham S.R. and his co-authors, who established in 2012 that sublingual immunotherapy is well tolerated by patients, reducing the symptoms of pollinosis and improving the quality of life (Durham *et al.,* 2012). Similar results were previously obtained in the work of other foreign scientists, where the vaccine was well tolerated by patients with minor local side effects, and the clinical manifestations of SLIT were a safe alternative for the parenteral type of immunotherapy and, moreover, were used fairly easily at home (Calderon *et al.,* 2011; Saltabayeva, 2016b; Saltabayeva *et al.,* 2017).

4. CONCLUSIONS:

Summarize the data discussed in the Results and Discussion showing the relevance of the work and how different it is from others researches. Also, point out the benefits and improvements that can be observed in order to develop new scientific standards that can change something in the related field.

Thus, a more frequent occurrence of both local and systemic adverse reactions during the parenteral type of immunotherapy compared with sublingual was reliably established. The favorable effect of ASIT on the course of concomitant allergic pathology manifested itself in a decrease in the frequency and severity of exacerbations of allergic diseases, which, of course, made it possible to reduce the volume of basic therapy. It should be noted that comparatively undesirable effects were more often noted when using parenteral ASIT in the form of systemic reactions, and with sublingual administration – more of a local character. However, local adverse events in most cases were resolved on their own, without the use of drug therapy and changes in treatment tactics. However, systemic adverse events, registered with parenteral form of ASIT, required the appointment of short courses of antihistamines and the use of local glucocorticosteroids.

Therefore, analyzing the above studies, were concluded that sublingual immunotherapy increases the safety of treatment and is a good substitute for the parenteral ASIT method, especially in pediatric patients, while having several advantages, such as a significant reduction in adverse reactions, high potency, and a convenient mode of administration, greater patient commitment and trust in treatment, and the elimination of infection transmission.

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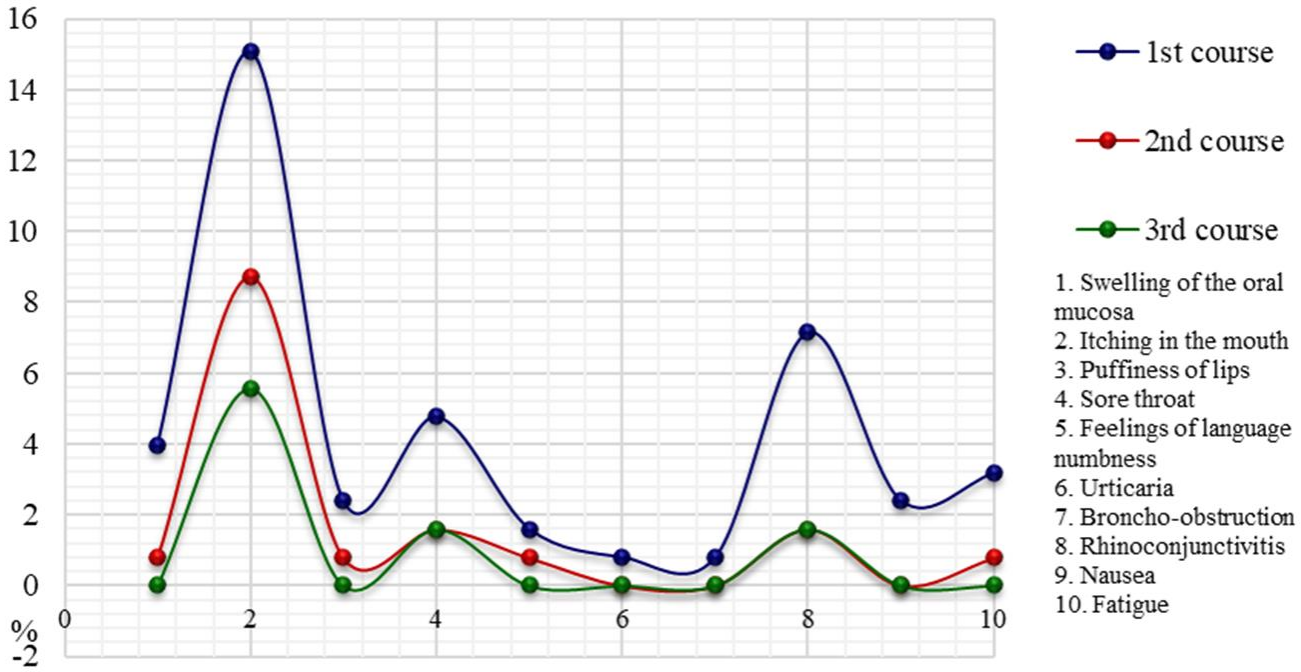

Figure 1. *Undesirable effects on the background of SLIT*

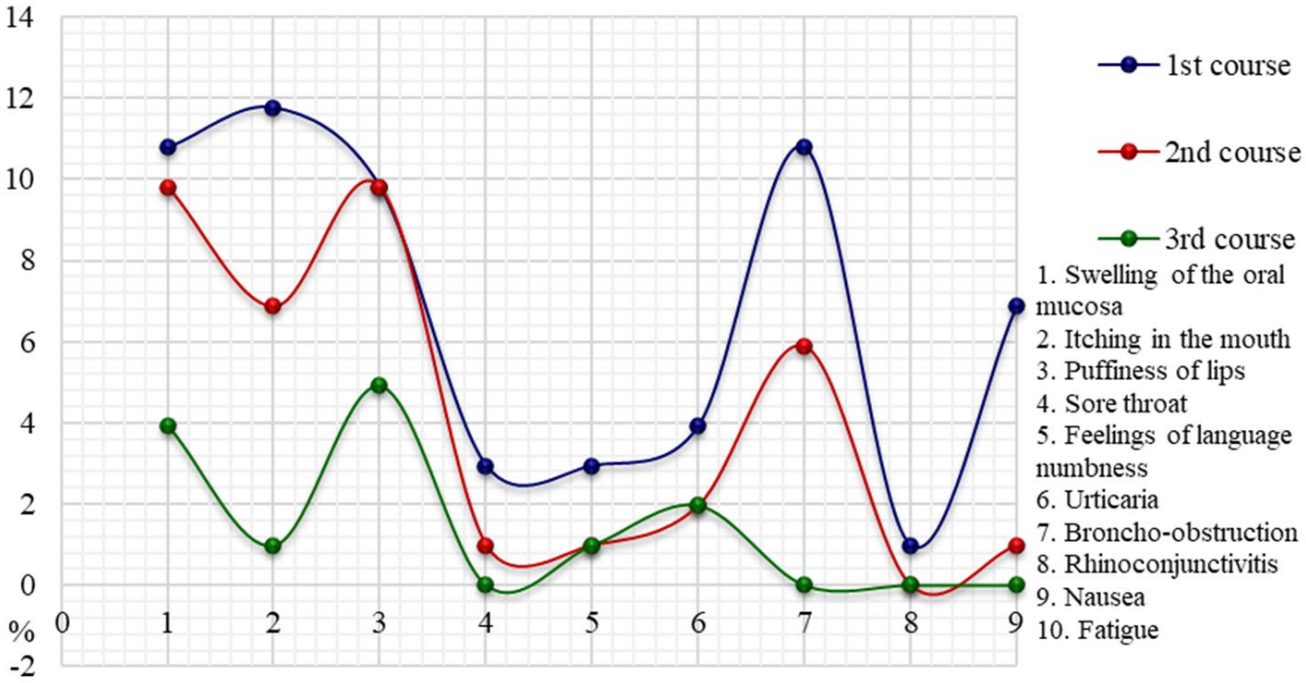

Figure 2. *Undesirable effects on the background of PIT*

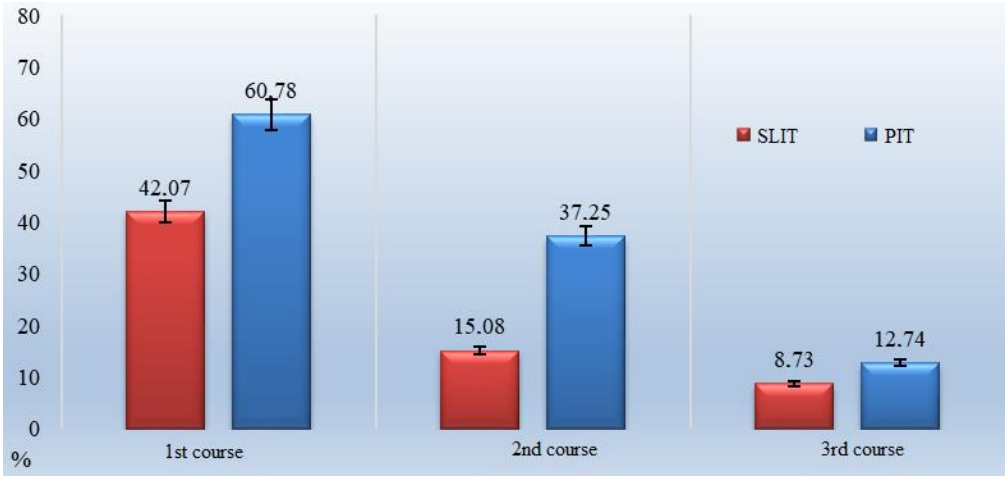

Figure 3. *Comparative dynamics of undesirable reactions on the background of SLIT and PIT*

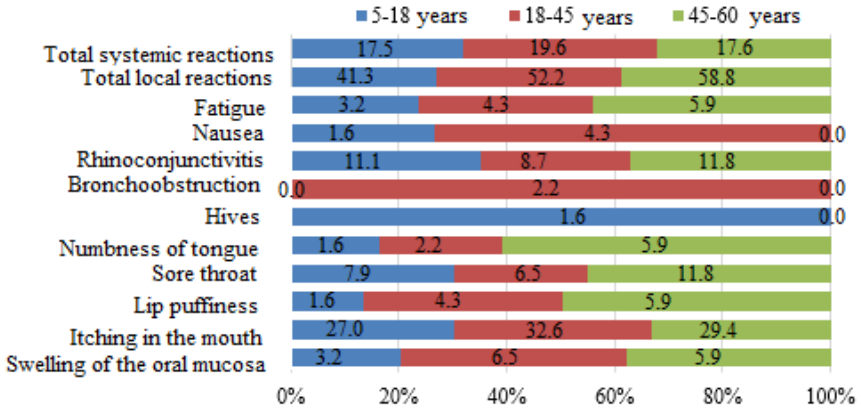

Figure 4. *Evaluation of local and systemic adverse events in patients of different age groups against the background of SLIT*

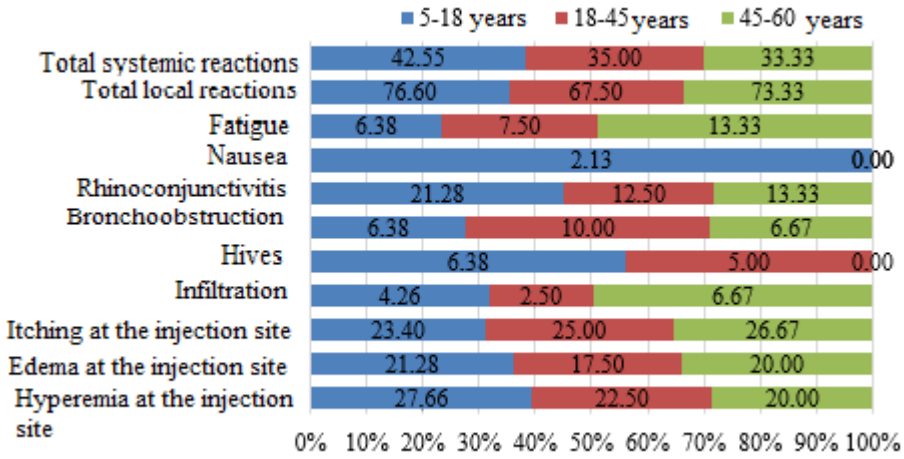

Figure 5. *Evaluation of local and systemic adverse events in patients of different age groups on the background of SLIT*

Table 1. *The frequency of local and systemic adverse reactions during sublingual immunotherapy in patients with pollinosis*

Adverse events	1st course SLIT N=126, (%)	2nd course SLIT N=126 (%)	3rd course SLIT N=126 (%)	P value
Local				
Swelling of the oral mucosa	5(3.97)	1(0.79)	0(0.00)	<0.001*
Itching in the mouth	19(15.08)	11(8.73)	7(5.55)	<0.001*
Lip puffiness	3(2.38)	1(0.79)	0(0.00)	<0.05
Sore throat	6(4.76)	2(1.59)	2(1.59)	<0.01
Feelings of numbness of the tongue	2(1.59)	1(0.79)	0(0.00)	<0.05
Total	35(27.78)	16(12.70)	9(7.14)	<0.001*
Systemic				
Hives	1(0.79)	0(0.00)	0(0.00)	<0.05
Bronchoobstruction	1(0.79)	0(0.00)	0(0.00)	>0.05
Rhinoconjunctivitis	9(7.14)	2(1.59)	2(1.59)	<0.001*
Nausea	3(2.38)	0(0.00)	0(0.00)	<0.05
Fatigue	4(3.17)	1 (0.79)	0(0.00)	<0.01
Total	18(14.29)	3 (2.38)	2(1.59)	<0.001*
Total	53(42.07)	19(15.08)	11(8.73)	<0.001*
*High statistically significant				

Table 2. *The frequency of local and systemic adverse reactions during parenteral immunotherapy in patients of the control group*

Undesirable effects	1st course SLIT N=102 (%)	2nd course SLIT N=102 (%)	3rd course SLIT N=102 (%)	P value
Local				
Hyperemia at the injection site	11(10.78)	10(9.80)	4(3.92)	<0.01
Edema at the injection site	12(11.76)	7(6.86)	1(0.98)	<0.001*
Itching at the injection site	10(9.80)	10(9.80)	5(4.90)	<0.05
Infiltration	3(2.94)	1(0.98)	0(0.00)	<0.05
Total	36(35.29)	28(27.45)	10(9.80)	<0.001*
Systemic				
Hives	3(2.94)	1(0.98)	1(0.98)	<0.05
Bronchus obstruction	4(3.92)	2(1.96)	2(1.96)	<0.05
Rhinoconjunctivitis	11(10.78)	6(5.88)	0(0.00)	<0.001*
Nausea	1(0.98)	0(0.00)	0(0.00)	<0.05
Fatigue	7(6.86)	1 (0.98)	0(0.00)	<0.01
Total	26(25.49)	10(9.80)	3(2.94)	<0.001*
Total	62(60.78)	38(37.25)	13(12.74)	<0.001*
* High statistically significant				