

Efficacy and Safety of Unique Natural Combination Spray for Symptoms Relief in Children with Allergic Rhinitis

Ostojic Olivera¹, Milosević Katarina^{2,3}, Sagić Lidija⁴, Djuretic A⁵, Zivanovic Snezana^{6,7}, Kostic Gordana^{8,9}, Ivana Filipovic¹⁰, Vekovic Vesna¹ and Zivkovic Zorica^{1,11*}

¹Children's Hospital for Lung Diseases and Tuberculosis, Medical Center "Dr Dragisa Misovic", Belgrade, Serbia

²University Children's Hospital Belgrade, Serbia

³Faculty of Medicine, University of Belgrade, Serbia

⁴Municipal Institute for Lung Disease and Tuberculosis Belgrade, Serbia

⁵Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia

⁶Children Clinic, Clinical Center Niš, Niš, Serbia

⁷Faculty of Medicine, University of Niš, Niš, Serbia

⁸Children Clinic, Clinical Center Kragujevac, Kragujevac, Serbia

⁹Faculty of Medicine, University of Kragujevac, Kragujevac, Serbia

¹⁰Hospital for Gynecology and Obstetrics, Medical Center "Dr Dragisa Misovic", Belgrade, Serbia

¹¹Faculty of Pharmacy, University Business Academy in Novi Sad, Novi Sad, Serbia

***Corresponding Author:** Zorica Zivkovic, Children's Hospital for Lung Diseases and Tuberculosis, Medical Center "Dr Dragisa Misovic", Belgrade, Serbia.

Received: January 27, 2021; **Published:** February 27, 2021

Abstract

Introduction and Objective: Allergic rhinitis (AR) is one of the common diseases among children. Through childhood, AR prevalence is between 30% to 40% in children and adolescents. It is usually underdiagnosed because the symptoms are nonspecific and accountable to recurrent colds. It has a negative impact on quality of life. The aim of this study is to evaluate the efficacy and safety of this natural nasal spray for symptoms relief in children with AR.

Patients and Methods: The study was conducted in the period from August 2017 to March 2018 as a multicentre, prospective study among 237 pediatric patients age 3 to 18 with allergic rhinitis. At the first visit, we took medical history data, demographic data, clinical symptoms (nasal congestion, itchy nose and eyes, sleepiness, duration of symptoms, time of occurrence), clinical examination was conducted and also allergy skin prick test and nasal swab. The children were given PropoMucil® allergy nasal spray (combination of standardized propolis with 12% of polyphenol and N-acetylcysteine, quercetin, thyme and eucalyptus essential oil and vitamin D3 and E; Abela Pharm, Belgrade, Serbia) to use it. Our patients used nasal spray, daily, for 30 days. At the second visit, patients fill out the questionnaire- about symptoms, therapy efficiency, favorability of spray taste, adverse effect.

Results: Out of the 237 patients, 60% were boys and 50% of children had up to 9 years. At the first visit, vast majority of the parents/ caregivers - 90% of them, reported nasal obstruction in children, nasal itching in 69% and sneezing in 68%, fatigue and sleepiness in 22%. The allergy test was performed in 94% participants.

Persistent type of AR had 58% children. Moderate type of AR had 58% children, and 42% had mild form. Only 3% of children previously did not receive any treatment, while 97% were treated with antihistamines and/or nasal corticosteroid therapy. After 30 days therapy with PropoMucil® allergy nasal spray, number of subjects with no nasal itching was 55% and no nasal congestion, 60%. 7% of children reported adverse effects: tingling nose, nasal bleeding, watery eyes, itchy nose, sneezing.

Conclusion: The combination propolis, N-acetylcysteine, quercetin, thyme and eucalyptus essential oil and vitamin D3 and E in nasal spray is a good choice for the treatment of allergic rhinitis in children. About 80% of parents said that this nasal spray improved overall health in their children.

Keywords: Allergic Rhinitis; Nasal Congestion; Children; Propolis; N-Acetylcysteine

Introduction

It is estimated that more than one third of population all over the world is currently suffering from at least one allergic disease [1,2]. Allergy incidence is increasing, especially in children and young adults, who are bearing the greatest burden of these trends [1,2].

Allergic rhinitis (AR) is an inflammation of the nasal mucosa caused by exposure to allergens which, after sensitization, trigger an inflammatory response mediated by immunoglobulin E (IgE) that may result in chronic or recurrent symptoms [4]. According to the recommendation of the Allergic Rhinitis and Its Impact on Asthma (ARIA) and the World Health Organization (WHO), its classification should take into account the duration and severity of symptoms, as well as quality of life (QOL) aspects [1,3]. In pediatrics, AR represents a global health problem and has a significant impact on the child's life. It is a prevalent pathology, reaching about 30% of the population, on average 13% to 21% of preschoolers, 15% of schoolchildren, and up to 40% of adolescents. [1-5] Individuals generally develop symptoms of AR before the age of 20 years, with approximately 40% of patients becoming symptomatic by 6 years of age [6]. The main symptoms of the AR include rhinorrhea, nasal obstruction and blockage, nasal itching and repetitive sneezing [6,7]. Nasal congestion is a hallmark of AR and is often the symptom patients find most troublesome and would like most to prevent [5,6]. Furthermore, typical sleep-related problems seen in AR, such as sleep-disordered breathing, sleep apnea, and snoring, are associated with nasal obstruction [7]. AR in the past, been considered trivial diseases but are increasingly recognized as having a major effect on quality of life (QOL). If is not properly controlled, AR can predispose sinusitis, otitis media, and hearing loss, with adverse consequences on school cognition [8]. Current studies have evidenced the negative impact of AR on the learning process, cognitive ability, memory and psychosocial relationships, as well as predisposition to behavioral disorders, such as restlessness, irritability, inattention, and daytime sleepiness [9-12]. These symptoms may impair the child's concentration and may adversely affect performance in a variety of settings. Children with AR experience practical issues (e.g. blowing nose repeatedly), limitations in outdoor or group activities that expose them to allergens, feelings of isolation, missed days of school. Children with AR who do not have asthma have also been found to experience better AR-related QOL than children with both conditions [12-16]. They are also associated with considerable economic burden. Data from the Asthma and Allergy Foundation of America indicate that in 2010 approximately US\$17.5 billion was spent on AR health-related costs, with affected individuals making 16 million physician visits on account of AR. A recent analysis put the total annual costs of AR at €1.3 billion annually in Sweden and, after extrapolation of the data to other European countries, at between €9.4 and €9.9 billion in Germany, France and the United Kingdom [11,17].

In childhood, AR is usually underdiagnosed because the symptoms are nonspecific and referable to recurrent colds. Reason for this is that early age is the period of life when viral infections are quite frequent [18]. Children with AR are also more likely to present with atopic eczema and asthma, coexisting in 50% to 60% of pediatric patients.

Sensitization to outdoor allergens can occur in allergic rhinitis in children older than 2 years; however, sensitization to outdoor allergens is more common in children older than 4 - 6 years. Clinically significant sensitization to indoor allergens may occur in children younger than 2 years [19,20].

Though AR is considered as a mild disorder, often being observed by parents/caregivers as an irritation rather than a disease, and frequently underdiagnosed, misdiagnosed and mistreated.

In Serbia, about 4.6% to 21% children had symptoms of AR. (ISAAC phase 3) [21]. Most of children with AR use pharmacotherapy, but still experience symptoms of the disease. Many parents do not give children full dosage/or at all, of prescribed therapy, because of fear of

adverse effects, especially considering topical corticosteroids. For these reasons, we have decided to examine the efficacy and safety of the natural preparation in the treatment AR.

Aim of the Study

The aim of this study were to show efficacy and safety of unique natural combination PropoMucil® allergy nasal spray (combination of standardized propolis with 12% of polyphenol and N-acetylcysteine, quercetin, thyme and eucalyptus essential oil and vitamin D3 and E; Abela Pharm, Belgrade, Serbia) in children with allergic rhinitis.

Materials and Methods

Our study was a real life prospective observational study. This multi center study was conducted at the following institutions: University Children's Hospital, Municipal Institute for Lung Diseases and Tuberculosis, and Children's Hospital for Lung Diseases and Tuberculosis, Medical Center "Dr Dragisa Misovic" in Belgrade, Institute for children and youth health care of Vojvodina, Novi Sad, Serbia, Clinical center in Kragujevac, Clinical Center in Niš, Serbia from August 2017 until March 2018. The protocol was approved by the Ethical Committees of the hospitals. Informed consent was obtained from all parents or caregivers of the participants. All patients included in the study were diagnosed with allergic rhinitis seasonal or perennial.

At the baseline patients or there parents or caregivers filled in the questionnaire that included: demographic data (age, gender), socio demographic and health data [29]. Afterwards they were asked also to complete Modified Pediatric Rhino conjunctivitis Quality of Life Questionnaire [23]. That questionnaire included: nose symptoms (nasal congestion, pruritus, sneezing, rhinorrhea, eye symptoms (redness, itching, edema, dryness) as well as practical problems (e.g. rub nose and eyes, blow nose, carry tissues), other symptoms (e.g. thirst, irritable, tired), and activity limitations. Medication score was also recorded for the following drugs: antihistamines, intranasal corticosteroids.

After physical examination skin prick tests (SPT) were performed according to published guidelines with a standard battery of glycerinated extracts (Institute of Virology, Vaccines and Sera TORLAK, Belgrade, Serbia). The following allergens were tested: house dust, dust mite (*Dermatophagoides* spp.), cockroach, mold, animal dander, pollens (tree, grass and weed). Histamine and saline were used as positive and negative controls, respectively. A drop of each allergen extract was placed on the volar surface of the forearm and was penetrated with a separate lancet. After 15 minutes, the wheal reaction was measured as the mean of the longest diameter and the diameter perpendicular to it. Reactions (mean wheal diameter ≥ 3 mm) were considered positive. Lung function test was performed using Jaeger, Pneumo Screen spirometry. Subjects were advised to avoid the use of the short-acting bronchodilator at least 12h before the test. FEV1 values were expressed as a percentage of predicted values. The children were given PropoMucil® allergy nasal spray (combination of standardized propolis with 12% of polyphenol and N-acetylcysteine, quercetin, thyme and eucalyptus essential oil and vitamin D3 and E; Abela Pharm, Belgrade, Serbia) to use it for one month, 4 sprays in every nostril per day. Propolis contained in PropoMucil® is free from allergens and gluten. N-acetylcysteine is of natural, non-human, non-animal origin obtained by fermentation from the special *E. coli* strain culture.

All patients were followed up during the six months from the beginning of the protocol. At the second visit - in the second month of follow up period patients were asked to refill the questionnaires. Nasal swab samples were collected for eosinophils counts and microbiology evaluation.

During the whole follow up period patients or their parents or caregivers are asked to report any kind of side effects.

Statistical analysis

The sample size was calculated with the software package G power. Descriptive and analytical statistical methods were used. The following descriptive variables were described: measures of central tendency (mean, median), measure of dispersion (standard deviation, interval of variation). Analytical statistical methods were used to test differences, parametric and nonparametric variables. Student’s t test and analysis of variance of repeated measurements were used. Chi square test, McNemar test, Mann-Whitney test, Wilcoxon test, Friedman test were also included. All data were analyzed in SPSS 15.0 software package. (SPSS Inc., Chicago, Illinois, USA).

Results

The study included 237 children, 144 boys (60%) and 93 girls (40%) The youngest participant was 3 years old and the oldest was 18 years old.

Nasal congestion was present in 90% children. Itching nose and sneezing were represented in a similar percentage (nasal itching in 69% and sneezing in 68% of children). Itching and watery eyes were present in less than half the children. Both nasal and ocular symptoms were improved during the follow up period particularly nasal congestion (Table 1).

Symptoms		First examination (% children)	Follow-up examination (% children)
Nasal congestion	No	10	68
	Yes	90	32
Itchy nose	No	31	82
	Yes	69	18
Sneeze	No	32	65
	Yes	68	35
Itchy eyes	No	55	75
	Yes	45	25
Swab nose	Negative	44	31
	Positive	7	4
	Not done	49	65

Table 1: Symptoms of children on the first and on the follow-up visit.

56.2% of children were affected by seasonal symptoms, with 43% symptoms lasting throughout the year, and in a small number of children, parents noted problems that are seasonal (likely to increase then) and last throughout the year or were unable to evaluate dependence of trouble from the season (Figure 1).

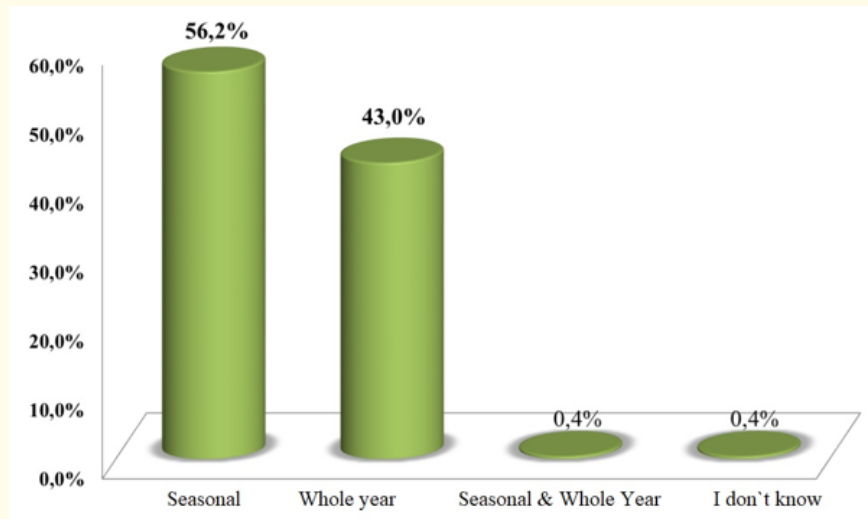


Figure 1: The timing of the occur of symptoms of allergic rhinitis.

From 233 children with allergic rhinitis, 58% had a persistent type of rhinitis, while others had an intermittent type. After assessing the severity of the disease, in most children (58%) a moderate type was recorded, and 42% mild. In 50% of children, the symptoms lasted up to 7 months (median 7 and interquartile range from 3 to 37.5 months). In one of the subjects, the symptoms lasted less than 1 month, while in 3 subjects the symptoms lasted 120 months.

Only 3% of children did not receive treatment, while the other 97% were on one of the recommended therapies. Approximately the same percentage of children was treated per os of antihistamine, nasal corticosteroid therapy or by a combination of previously mentioned therapies. Only 1% had another combination of therapies (Figure 2).

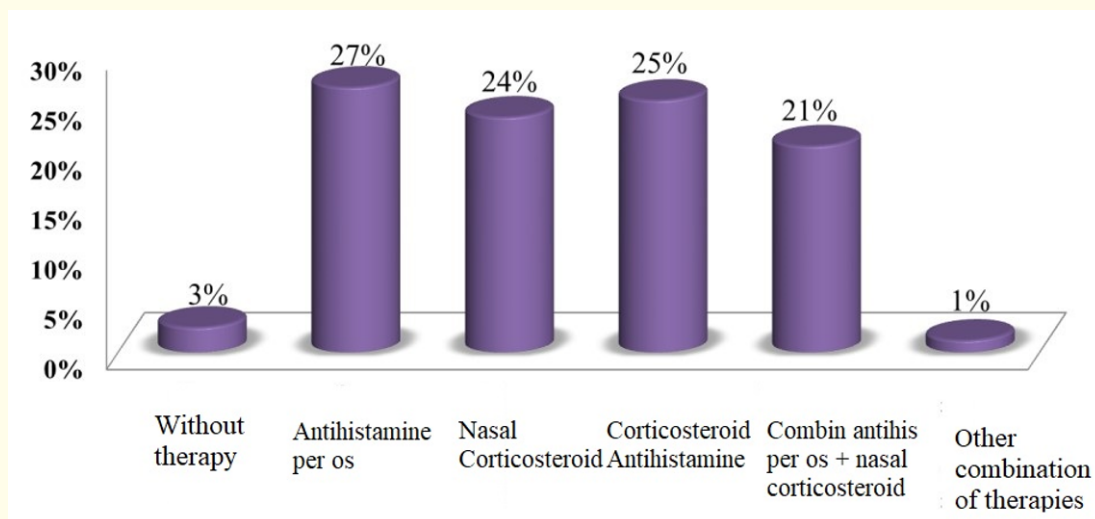
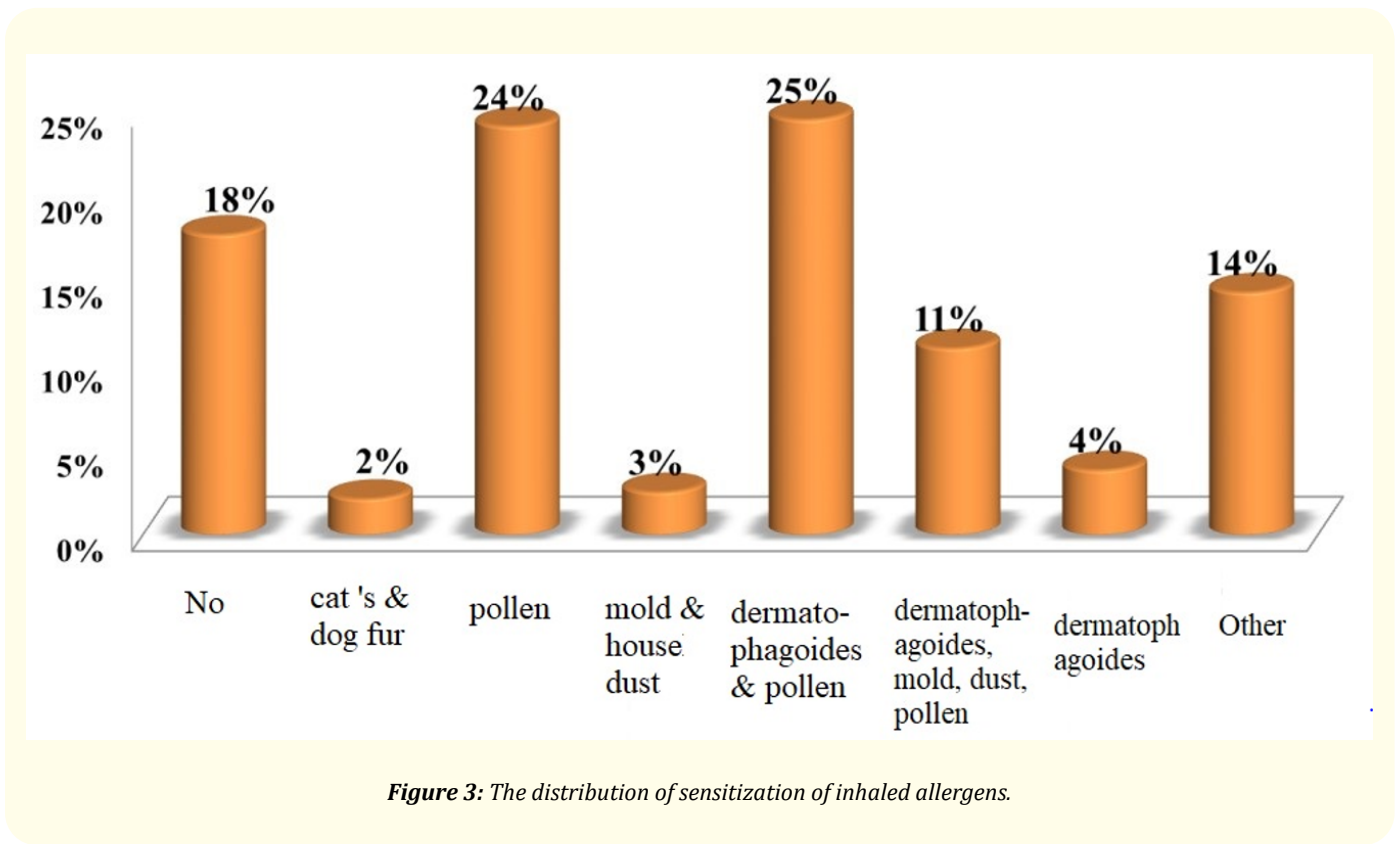


Figure 2: Therapy of allergic rhinitis.

The allergy test was made in 94% of children. Sensitization on inhaled allergens, such as cat 's and dog fur, pollen trees and grass, house dust, cockroaches, pollen of ambrosia, dust mite and feathers have been identified. 39% children were polysensitized (to more than two allergens) 25% of children were sensitized to house dust mite and pollen and on pollen only 24% of children. Monosensibilisation was identified in a small percentage of children (house dust mite in 4%, worms and house dust in 3% and cat or dog hair in 4% of children) (Figure 3).



Nasal swabs were taken from children for microbiological testing and eosinophils testing. The elevated level of eosinophils were present in 33% of children. Microbiological analysis of nasal swab was done in only 51% of children and was positive in 7% of respondents. 50% of children had FEV1 up to 90% or less, and FVC up to 81% or less.

Assessed the presence of the congestion and itching of the nose in two points. A comparison was made with McNemar’s test. 27% of the examinees did not have itchy nose at all, while 14% of the examinees had a runny nose in both points. It is interesting that in the majority of subjects (55%) itching of the nose was lost after 30 days, while 4% of parents said that these symptoms occurred after therapy. An increase in the number of subjects with no nasal itching after 30 days was statistically significant ($p < 0,001$) (Figure 4).

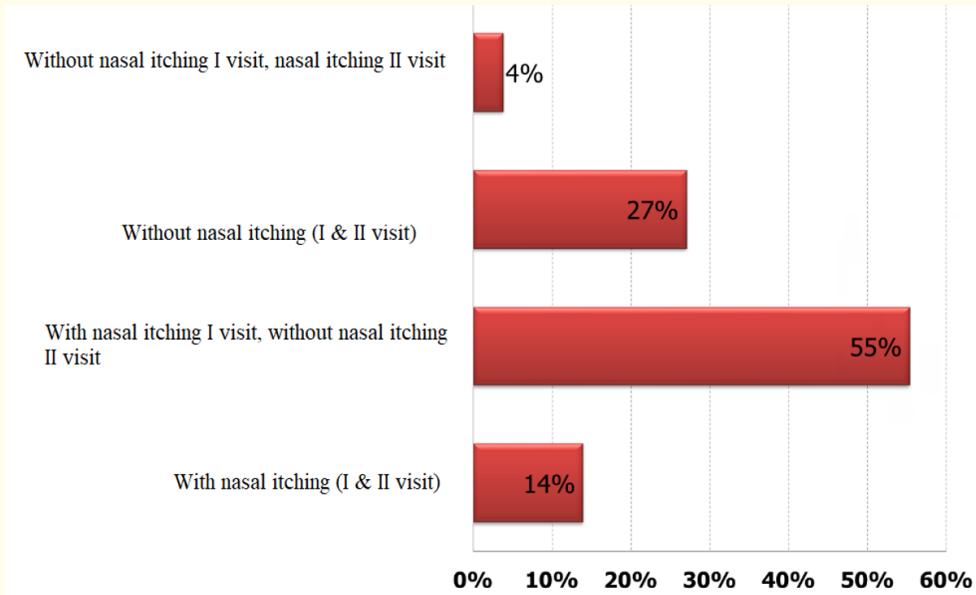


Figure 4: Percentage share of the itchy nose between first and second visit

In the vast majority of subjects who reported nasal congestion (60%), this problem was lost after 30 days. In 30% of children nasal congestion were persistent, while in 2% of patients developed after 30 days although it was not present during the first visit. 8% of patients did not have a nasal congestion in the first or second visit. Growth of the subjects without nasal congestion and decrease of subject with nasal congestion after 30 days was statistically significant ($p < 0.001$) (Figure 5).

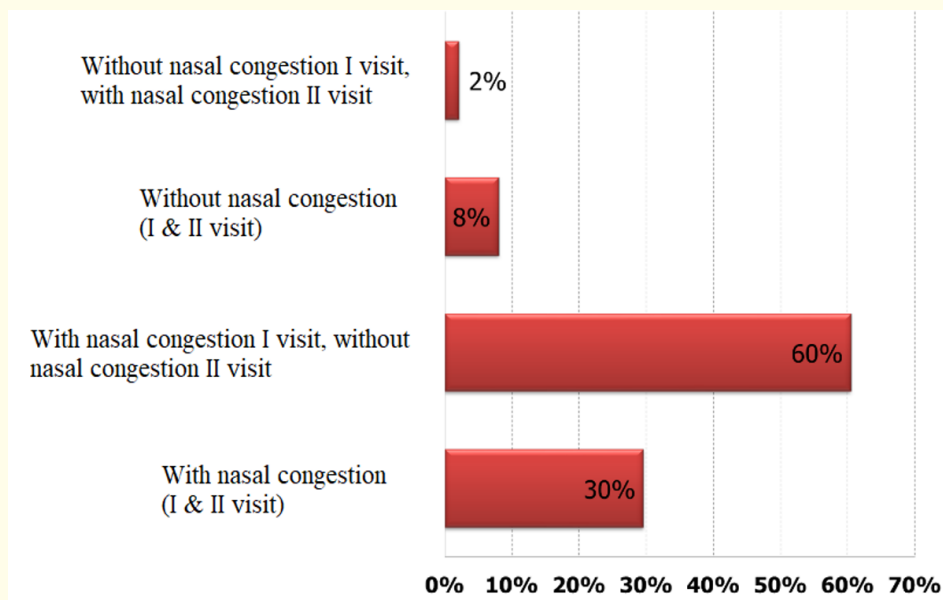


Figure 5: Percentage of the nasal congestion between first and second visit.

93% of parents did not notice adverse effects in children. Only 7% of children reported adverse effects. The side effects reported by study participants were: tingling nose, nasal bleeding, watery eyes, itchy nose, sneeze.

Discussion

It is known that the clinical expression of respiratory allergies tends to change over time, according to a “natural history”, the so-called “atopic march”. In the typical sequence, allergic rhinitis often precedes the onset of asthma and, therefore, it can be considered a risk factor for the development of allergic asthma [29-31]. The data obtained in this study show that almost 59% of children with symptoms of AR have a diagnosis of asthma. In addition, there is often the tendency to develop new sensitivities along time: the natural history of sensitizations begins usually with foods, continues with environmental allergens (usually dust mites) and ends with pollens. In almost 70% of our patients, allergens such as pollen have been identified either alone or in combination with another allergen.

Therapy used in the prophylaxis of asthma exacerbation in children, mostly were inhaled corticosteroids (39%), followed by fixed combination IKC and LABA (26%), LTRA and a combination inhaled corticosteroids and LTRA were less (15% and 13%).

Environmental control is of paramount importance in the treatment of these diseases, as recommended in national and international consensus papers. The main control measures on prevention are included avoid contact with allergens.

Topical nasal corticosteroids and antihistamines are commonly prescribed therapy for AR [24-26]. Nasal corticosteroids act directly on the nasal mucosa and represent the most effective anti-inflammatory agents used for the treatment of pediatric allergic rhinitis [27]. However, safety of these compounds remains controversial and main concerns derive from dose-related systemic adverse effects associated to long-term treatments, such as suppression of adreno-cortical function, growth and bone metabolism [28]. Adherence to treatment is the major problem of allergic disease, especially in allergic rhinitis. Self-management strategies should be considerably expanded. In our study approximately 70% of children was treated with nasal corticosteroid therapy only or by a combination with antihistamines before included on investigation [29]. Decongestants and immunotherapy, equally present varying levels of safety and tolerability issues in children [30]. Pharmacotherapy of AR in children requires, therefore, great attention to dosing and the avoidance of the many adverse effects related to standard therapies. That is why there is a growing need for alternative or adjuvant treatments for the relief of AR symptoms, in aim to reduce the amount of pharmacological therapy in pediatric field [31,32]. Treatment with plants is the comparison of the pharmacological properties of chemical medicines in interaction with herbs and natural products. As a holistic and natural therapy, phytotherapy became a leadingly important alternative therapeutic option after unsatisfactory response to conventional treatment.

Propolis has anti-inflammatory and antibacterial properties, especially against *Staphylococcus aureus* [33]. The mechanism of antimicrobial activity of propolis is complex and can be explained by synergic action of phenol and other compounds, mostly the flavonoids pinocembrin, galangin and pinobanksin. It has a strong action on the growth of gram-positive bacteria.

N-acetyl is a derivative of the amino acid L-cysteine, the thiol (sulfhydryl) group provides it with an anti-oxidative effect thus reducing the amount of free radicals. It is used as a mucolytic agent. Its mucolytic action is achieved by decomposition of disulphide bonds in mucopolysaccharides binding the proteins found in mucus (mucoproteins).

Proinflammatory cytokine IL-1 stimulates human leukemic mast cells (HMC-1) to release newly synthesized IL-6. Quercetin is a bioflavonoid found in red wine, grapefruit, onions, apples, black tea, and, in lesser amounts, in leafy green vegetables and beans, that was

recently shown to strongly inhibit IL-6 secretion in response to allergic stimulation, and it can stabilize mast cells in a way that helps lower stress induced anxiety and allergic reactions, has an antioxidant and anti-inflammatory activity [19]. In addition to flavonoids, propolis also contains caffeic acid phenylethyl ester, which inhibits the release of arachidonic acid from the cell membrane, suppressing the COX1 and COX2 enzymes, and the COX2 gene expression.

According to this reasons we were given to children with AR natural product, PropoMucil® allergy nasal spray (combination of standardized propolis with 12% of polyphenol and N-acetylcysteine, quercetin, thyme and eucalyptus essential oil and vitamin D3 and E. Combination of standardized propolis with 12% of polyphenol and N-acetylcysteine demonstrated good efficacy and safety in the treatment of acute respiratory infections in children [34].

We had observed improvement of the AR in 84% their children. In 15% of children there were no changes compared to the first review and 1% experienced deterioration. If, as the main symptoms of allergic rhinitis, itching and nasal congestion are compared at the beginning of the study, and after 30 days of using nasal spray, a statistically significant reduction in the percentage of subjects with itching and nasal congestion (55%, or 60% reduction in the number of subjects) is observed.

We reported only mild adverse effects in 7% of children. The side effects reported by study participants were: tingling nose, nasal bleeding, watery eyes, itchy nose, sneeze. According this data we concluded that PropoMucil® allergy nasal spray is safe to use in children with AR.

Conclusion

The combination of propolis and N-acetylcysteine in PropoMucil® nasal spray is a good choice for the treatment of allergic rhinitis in children.

Approximately 80% of parents said that this nasal spray led to an improvement in the condition of the child. PropoMucil® spray for allergy has good clinical efficacy in reduction the main symptoms of AR. The demonstrated bactericidal and antiviral properties of the product can reduce irrational use of antibiotics, especially for children. According a small percent mild adverse effect, we concluded that PropoMucil® allergy nasal spray is safe to use in children in all aged group. Our study confirmed its efficacy and safety.

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Volume 10 Issue 3 March e2021

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