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EFFECT OF NASAL CORTICOSTEROIDS ON OXIDATIVE STRESS PARAMETERS IN CHILDREN WITH ALLERGIC RHINITIS

Ivana Arnaudova Danevska[1], Tatjana Jakjovska[1], Emilija Atanasovska[2], Marija Petrushevska[2], Pavlina DzekovaVidimliski[3], Svetlana Krstevska Balkanov[4], Trajan Balkanov[2], Dragica Zendelovska[2]

[1]Ss Cyril and Methodius University in Skopje, Faculty of Medicine, Institute for Respiratory Diseases in Children, RN Macedonia

[2]Ss Cyril and Methodius University in Skopje, Faculty of Medicine, Institute of Preclinical and Clinical Pharmacology and Toxicology, RN Macedonia

[3]Ss Cyril and Methodius University in Skopje, Faculty of Medicine, University Clinic for Nephrology, RN Macedonia

[4]Ss Cyril and Methodius University in Skopje, Faculty of Medicine, University Clinic for Hematology, RN Macedonia

Abstract

Oxidative stress (OS) is a result of an imbalance between the production of free radicals and the antioxidant defense mechanisms in the organism. Allergic rhinitis (AR) is characterized by chronic inflammation and increased presence of eosinophils, basophils and mast cells in nasal secretions and mucosa. Stimulation of these cells results in production of free radicals (reactive oxygen metabolites). The aim of this study was to determine the level of OS and antioxidant capacity in children with AR after 8 weeks treatment with nasal corticosteroid (NCS).

Thirty children with AR (mean age 8.3 ± 2.9 years) were included. The FRAS 5 Bravo system was used to determine the OS parameters. Demographic characteristics, medical history, children's living conditions and eating habits were obtained from the questionarrie. Anthropometric measurements, absolute number of eosinophils in the peripheral smear and eosinophils in nasal smear were performed in each child.

The mean value of blood concentration of serum peroxides (d-ROMs) was 403.4 ± 91.3 U. Carr, while the mean value of OS index was 95.1 ± 45.9. After 8 weeks of treatment with NCS, the mean values were 337.6 ± 71.9 U. Carr, and 53.6 ± 28.3, respectively. Both parameters had significantly lower values ($p<0.05$) compared to those before the initiation of NCS therapy. After treatment, a significant improvement in the symptoms score of AR was detected ($p<0.05$).

NCS therapy makes asignificant improvement of the symptoms and a considerable reduction in the OS in children with AR.

Keywords: allergic rhinitis, children, oxidative stress, d-ROMs, PAT, OSI

Introduction

Oxidative stress is an important part of aging processes and many other pathological conditions and processes [1]. It is a result of an imbalance between the production of pro-oxidants (ROS-reactive oxygen species) and the antioxidant defense mechanisms in the organism. Endogenous sources of ROS are cell organelles (mitochondria, peroxisomes, endoplasmic reticulum), various enzymes and enzyme complexes (e.g., cytochrome P450, nicotinamide adenine dinucleotide phosphate-oxidases, nitric oxide synthetase, xanthine oxidase), certain cells (especially phagocytes, activated eosinophils and neutrophils, monocytes and macrophages, airway epithelial and smooth muscle cells, endothelium) and others (e.g., heme proteins, metal ion reactions).

On the other hand, there are also many exogenous sources of ROS, such as cigarette smoke, ultraviolet light, ionizing radiation, pollutants, ozone, organic solvents, metals, and some drugs (e.g., chemotherapeutic agents). Both endogenous and exogenous sources of ROS can play an important role in the pathogenesis and exacerbation of various inflammatory conditions, especially with the continuous accumulation of oxidative changes in biomolecules [2-6].

Allergic rhinitis (AR) is an inflammatory disorder of the nasal mucosa that results from an allergic immune response to inhaled allergens in sensitized individuals. Allergic immune cascade in the nasal mucosa can cause symptoms of varying severity and duration. These include nasal congestion/obstruction, rhinorrhea, itchy nose and/or sneezing, as well as conjunctival symptoms (itchy eyes, watery eyes, conjunctival congestion, haemosis, and periorbital edema). In addition to local symptoms, allergic rhinitis also is presented with general symptoms such as fatigue, impaired concentration, and decreased productivity [7].

AR is a disease characterized by increased presence of eosinophils, basophils and mast cells in nasal secretions and nasal mucosa. Immune or non-immune stimulation of these cells results in the production of ROS such as superoxide anion, hydrogen peroxide and hydroxyl radicals.

The most important cells involved in the late phase of AR are eosinophils. In addition to tissue destruction, cytokines, chemokines, and cations released by activated eosinophils also increase inflammation through autocrine and paracrine pathways. Cytokines released by eosinophils in the late phase of the reaction play a major role in ROS production. Oxidative stress is thought to play an important role in the prolonged course of inflammation after this stage [8-10].

There are many studies that describe the role of oxidative stress in the pathogenesis of AR, but the number of researches that refer to the capacity of AR treatment in terms of reducing oxidative stress is limited [11-14].

The aim of this study wasto determine the level of oxidative stress parameters in children with AR after 8 weeks of treatment with nasal corticosteroid (NCS).

Material and methods

Study design (Patients)

The study was approved by the Ethics Committee of the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia. It was conducted from March 2021 till March 2022 at the Institute for Respiratory Diseases in Children in Skopje and at the Institute of Preclinical and Clinical Pharmacology with Toxicology at the Faculty of Medicine in Skopje. The study included children with AR of both sexes, at the age between 4 and 14 years. They had a positive skin prick test (SPT) for at least one inhaled allergen, presence of at least 2 symptoms of allergic rhinitis (local: nasal congestion/obstruction, rhinorrhea, sneezing, itchy nose and itchy eyes, or general symptoms: disturbed sleep and negative effect on physical activity).

Clinical characteristics and laboratory data

A study-specific questionnaire was prepared that included demographic characteristics (place of residence, ethnicity, etc.), medical history, children's living conditions (heating, gas cooking, passive smoking, animals in the households, frequency of passing trucks on the street of living during working days) and eating habits.

According to the anthropometric measurements (body height, body weight), body mass index (BMI) was calculated using the standard formula and expressed as weight (kg)/height (m^2). International BMI cut-off points established by Cole et al. [15] were used for overweight and obesity by gender, for ages between 2 and 18 years, defined BMI over 25 kg/m^2 for overweight and 30 kg/m^2 for obesity aged 18 years.

The scoring of the symptoms of AR was done by scoring local and general symptoms. A 3-point response scale was used for scoring of all individual items (never, rare, often). Based on the scoring of the symptoms, patients were divided into 3 categories:

- mild AR (2-4 points)
- moderately severe AR (5-7 points, of which at least 1 is a general symptom)
- severe AR (> 7 points, of which at least 1 is a general symptom).

The percentage of eosinophils in nasal secretions was determined by the standard procedure [16]. In all study participants blood was taken in order to determine the absolute number of eosinophils in peripheral smear.

Method for determination of d-ROMs, PAT and Oxidative stress index

In children with AR, serum sample was collected and analyzed after collection. The oxidative stress index was determined with the FRAS 5 Bravo system (H&D srl - Parma, Italy). d-ROMs test is a photometric test that allows to assess the pro-oxidant status in a biological sample by measuring the concentration of peroxides. It is expressed in U. Carr (1 U. Carr = 0.08 mg H_2O_2/dl), a unit of free radical scales used only by international scientific community. The normal d-ROMs reference values are 250–300 U. Carr. PAT is a test which can be used to determine antioxidant power, iron reducing (both scavenger and antioxidant haematic concentration), expressed in U. Carr (1 U. Carr = 1.4 μmol/L Vitamin C). The reference values of the PAT test are 2200–2800 U. Carr. The results obtained from the d-ROMs and PAT test, the system summarizes in one value - oxidative stress index (OSI) with normal reference values less than 40.

Statistical analysis

Statistical analyses were performed using Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA). The parametric variables were presented as mean value ± standard deviation. The comparison of variables in children with AR before and after 8 weeks of NCS treatment was done with the Student's t-test. A value of $p<0.05$ was considered statistically significant.

Results

A total 30 children with AR (mean age 8.3 ± 2.9 years) were included. There was no presence of co-existing medical condition (cardiac, endocrinological, gastrointestinal, hematological, hepatic or renal); no medication was used and nobody participated in another clinical study in the last 2 months.

The anthropometric characteristics of patients, gender, body weight, body height and BMI, are shown in Table 1.

Table 1. Anthropometric characteristics of patients: gender (M-male, F-female), body weight, body height and BMI.

	Children with AR
	Number (n)
Gender (M/F)	20/10
	X±SD
Age (years)	8.3 ± 2.9
Weight (kg)	33.9±15.2
Height (cm)	133.7±17.9
BMI (kg/m^2)	18.2±4.0

Male gender predominated among the subjects,the median value of BMI was 18.2 ± 4.0 and it is slightly under the cut-off point for overweight.

The results of symptoms scoring for AR, percentage of eosinophils in nasal secretion, absolute number of eosinophils in peripheral smear, OS parameters in children with AR before and after 8 weeks of NCS treatment are shown in Table 2.

Table 2. Scoring of symptoms of AR, percentage of eosinophils in nasal secretion, absolute number of eosinophils in peripheral smear, OS parameters in children with AR before and after 8 weeks of NCS treatment.

Children with AR	Before NCS treatment	After NCS treatment	p
	X±SD	X±SD	
Symptoms (score) Local General	6.8±2.0 1.0±0.8	2.6±2.2 0.2±0.4	<0.001 <0.001
Total	7.9±2.5	2.8±2.3	<0.001
Eosinophils in nasal secretion (%)	8 ± 15	3 ± 7	0.091
Absolute number of eosinophils in peripheral smear (number/mm^3)	446.3 ± 331.4	320.3 ± 227.3	0.091
d-ROMs (U. Carr)	403.4 ± 91.3	337.6 ± 71.9	0.003
PAT (U. Carr)	2935.2±939.1	2663.7 ±491.3	0.166
OSI	95.1 ±45.9	53.6 ±28.3	<0.001

According to the severity of the symptoms in children with AR, the mean symptom score was 7.9±2.5, which is classified as severe AR. The mean value of the eosinophils percentage in nasal secretions was 8 ± 15%.

The mean value of concentration of serum peroxides expressed through the d-ROMs test in children with AR was 403.4 ± 91.3 U. Carr, which is a high level of oxidative stress. The mean value of the concentration of water-soluble antioxidants in the serum (PAT test) was 2935.2 ± 939.1 U. Carr, which is within a very high value. The mean value of OSI was 95.1 ± 45.9, which according to the stated reference values is high.

After 8 weeks of treatment with NCS, a significant improvement in the symptoms of AR was detected. The level of serum peroxides was 337.6 ± 71.9U. Carr, which is a low level in the d-ROMs test. The mean value of the concentration of water-soluble antioxidants in the serum (PAT test) was 2663.7 ± 491.3U. Carr, which is a normal value. The OSI was 53.6 ± 28.3, which was within the borderline level. Both parameters, d-ROMs and OSI, had significantly lower values compared to those before the initiation of NCS therapy, $p=0.003$ and $p<0.001$, respectively.

Data obtained from the questionnaire referred to demographic characteristics, living conditions of the children, atopic characteristics and eating habits are presented in Table 3. The majority of patients were Macedonians, lived in the city, were exposed to passive smoking. Half of them had a parent with a university degree. Data regarding living conditions showed a significant exposure to truck traffic, but not on indoor air pollution by gas cooking, heating and exposure to pets. Regarding the atopic characteristics of the subjects, positive family history of atopy, history of atopic dermatitis, positive skin tests to inhalant allergens were documented, but not in history of asthma, food and drug allergy. With reference to the eating habits, we observed frequent baked or boiled food, white bread, red meat, fruit and vegetables intake and natural juices (Table 3).

Table 3. Demographic characteristics, living conditions, atopic characteristics and eating habits of children

Questionnaire	AR (N=30)	
	n (%)	n (%)
Place of residence (city/village)	**25 (83.3)**	5 (16.7)
Ethnicity (Macedonian/Albanian)	**23 (76.7)**	7 (23.3)
Mother's education - university degree (yes/no)	15 (50)	15 (50)
Father's education - university degree (yes/no)	15 (50)	15 (50)
Type of heating in the home (central or electricity / air conditioning)	**17 (56.7)**	13 (43.3)
Gas cooking in the home (yes/no)	4 (13.3)	**26 (86.7)**
Passive smoking in the home (yes/no)	**19 (63.3)**	11 (36.7)
Frequency of passing trucks on residential street during weekdays (never/sometimes)	11 (36.7)	**19 (63.6)**
Animals in home (yes/no)	12 (40)	**18 (60)**
Family history for allergy (yes/no)	**24 (80)**	6 (20)
Atopic dermatitis (yes/no)	13 (43.3)	**17 (56.7)**
Asthma (yes/no)	4 (13.3)	**26 (86.7)**
Drug allergy (yes/no)	2 (6.7)	**28 (93.3)**
Food allergy (yes/no)	5 (16.7)	**25 (83.3)**
Skin prick test (yes/no)	**29 (99.7)**	1 (0.3)
Clinically significant disease (yes/no)	0 (0)	**30 (100)**
Use of medicines (yes/no)	4 (13.3)	**26 (66.7)**
Use of nasal topic corticosteroids in the last 2 months (yes/no)	5 (16.7)	**25 (83.3)**
Type of food preparation (baked or boiled/fried)	**20 (66.7)**	10 (33.3)
Spicy food (yes/no)	14 (46.7)	**16 (53.3)**
Fast food (yes/no)	10 (33.3)	**20 (66.7)**
Bread (white/integral)	**24 (80)**	6 (20)
Juices (carbonated/natural)	5 (16.7)	**25 (83.3)**
Fruit intake (1-2 times a week/ ≥ 3 weeks)	10 (33.3)	**20 (67.7)**
Vegetable intake (1-2 times a week/ ≥ 3 weeks)	9 (30)	**21 (70)**
Fish intake (1-2 times a week/ ≥ 3 weeks)	**29 (99.7)**	1 (0.3)
Red meat intake (1-2 times a week/ ≥ 3 weeks)	6 (20)	**24 (80)**
Cereals intake (1-2 times a week/ ≥ 3 weeks)	**26 (66.7)**	4 (13.3)
Pasta intake (1-2 times a week/ ≥ 3 weeks)	**26 (66.7)**	4 (13.3)

Discussion

AR is an inflammatory disorder of the nasal mucosa as a result of IgE-mediated hypersensitivity after contact with a potent allergen. It usually involves the upper respiratory tract and the conjunctiva, sometimes the lower respiratory tract, and may coexist with asthma in the same patient [17].

The rate of production and removal of free radicals is balanced and is called oxidative balance. As long as the oxidative balance is maintained, the organism is not affected by free radicals. An increased rate of free radical formation or a decreased rate of free radical removal leads to a disruption of this balance, so-called oxidative stress, which results in tissue damage [18].

While NCS are recommended as a first-line treatment for AR, oral antihistamines, leukotriene receptor antagonists, and oral steroids are other alternative treatment options [19].

The NCS beclomethasone, flunisolide, budesonide, fluticasone, and mometasone are the most effective options in the treatment of AR [20, 21]. They reach high concentrations in the receptor areas of the nasal mucosa and have minimal systemic negative effects. Their effect is observed 7-8 hours after the administration of an intranasal dose, while the maximum effect is achieved in about 2 weeks from the start. They are effective for all symptoms of AR, well tolerated, and adverse effects are rare and similar to placebo [21].

A study by Kahveci et al. investigated the effect of AR therapy on TOS (Total Oxidative Status) and TAS (Total Antioxidative Status) in adult patients with AR. Either a nasal steroid alone (momethasone furoate), or a combination of a nasal steroid and an oral antihistamine (momethasone furoate + rupatidine fumarate) was administered. It was determined that there was a more significant reduction in TOS levels in the group that received both a nasal steroid and an oral antihistamine.

Although it has been concluded that combined therapy is more effective in AR and reduces oxidative stress in the organism, it should also be taken into account that the use of oral antihistamines can have a direct antioxidant effect by binding or removing free radicals [11].

Our study is the first that compares the level of OS in children with AR before and after 8 weeks of treatment with NCS (momethasone furoate). In the literature, there are studies about the effect of the treatment of AR on the parameters of OS in adult patients. Gratziou et al. investigated OS through a non-invasive method by determining isoprostane-8, Leukotriene B_4 and nitrates in exhaled breath condensate (EBC) in adult patients with AR with/without concomitant asthma. They determined a significant reduction of isoprostan-8 and Leukotriene B_4 after 1 month of treatment with nasal fluticasone propionate 100 μg in each nostril [12].

Similarly, elevated levels of cysteinyl leukotrienes in the EBC of adults with AR with/or without concomitant asthma were significantly reduced after 2 weeks of treatment with 100 μg nasal fluticasone propionate in each nostril once daily [13].

On the other hand, treatment with nasal triamcinolone reduced hydrogen peroxide in EBC of adult patients with AR [14].

Conclusion

Our study indicates that exposure to allergens induces oxidative stress in children with allergic rhinitis, but after 8 weeks of treatment with nasal corticosteroids there is a significant improvement in the symptom score and a considerable reduction in the oxidative stress index even without any clinical symptoms of involvement of the lower respiratory tract. Moreover, the evaluation of markers of oxidative stress can be a useful tool in investigating the pathogenesis of allergic airway diseases as well as their response to treatment.

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