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Efficacy of Speleotherapy on Atopic Bronchial Asthma in Children

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ABSTRACT

Objective: Despite stunning advances in drug treatment, the present modern drugs that are used in the treatment of bronchial asthma don't always achieve complete control over the disease. It may be useful to get support from complementary and alternative medicine (CAM) in such cases. CAM is understood as a non-traditional treatment, one of the varieties of which is speleotherapy. With the purpose of studying the therapeutic effect of speleotherapy in children, a treatment of speleotherapy was conducted for 50 children and adolescents suffering from atopic bronchial asthma.

Materials and Methods: To evaluate the effectiveness of speleotherapy, the following research methods were used: Spirometry method was used to assess the ventilation function of the lungs, nitric oxide in exhaled air was measured for the assessment of airway inflammation, and laboratory examination of patients were evaluated including Interleukin (IL)-5, IL-13 and Interferon-gamma (IFN-γ) in serum by using enzyme-linked immunosorbent assay (ELISA).

Results: As a result of the speleotherapy, patients improved their external respiratory function. The study also showed a positive impact with speleotherapy on exhaled nitric oxide and cytokine parameters in children with mild and moderate atopic bronchial asthma.

Conclusion: Speleotherapy, as a method of medical rehabilitation for patients with bronchial asthma, leads to a decrease in the number of attacks, reduces the use of bronchodilators, and improves the indicators of the function of external respiration.

Keywords: Allergy, asthma, children, nitric oxide, speleotherapy, spirometry

INTRODUCTION

Asthma is a chronic inflammatory disorder that affects the airways and causes coughing, chest tightness, shortness of breath, and wheezing. Atopic (allergic) asthma is the most common type of asthma in children and characterized by airway hyper-responsiveness to an allergen (1, 2). This form of asthma develops due to Immunoglobulin E (Ig E)-type hypersensitivity reactions, generally in response to inhaled allergens. The airways of individuals with allergic asthma are infiltrated by activated T lymphocytes, mast cells, eosinophils, and other cells that are involved in type 2 inflammation (3, 4). Exposure to a variety of trigger factors results in the contraction of smooth muscle of airways and subsequently asthma attacks.

There are many international recommendations and guidelines for effective asthma treatment and management. Currently, there are multiple advanced medications that are used in the treatment of bronchial asthma. Despite this, full control of the disease is not always achieved. In such cases, non-pharmacological treatment and medical rehabilitation must be applied. Complementary and alternative medicine (CAM) is the term used to refer to unconventional treatment (5, 6). Speleotherapy is one of the CAM options for an allergic form of bronchial asthma. Speleotherapy is an adjuvant therapy for asthma in caves and salt mines that is only available in certain areas of the world (7, 8).

These caves are characterized by a specific microclimate (speleoclimate), that is associated with stable temperature, absence of irritants, pollutants, and allergens, high

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humidity, and specific ratio of microelements such as Na^{+}, Cl^{-}, Mg^{+2} and Ca^{+2} ions (9, 10). Studies revealed that microclimate has a beneficial effect on the functioning of the respiratory system of asthmatic patients and provides bronchodilation and mucolytic effects, hyposensitivity, immunoprotective, and restorative effects. All this makes it possible to widely use speleotherapy in pediatrics (11).

MATERIALS AND METHODS

Study Group

The study was approved by the Ethics Committee (Protocol No: 28) of Azerbaijan Medical University. Parents signed a consent form for their children to participate in this study.

To investigate the therapeutic effects of speleotherapy in bronchial asthma, new research was conducted on children in Azerbaijan Nakhcivan "Duzdag" Physiotherapy Center. This study included a test group that comprised 50 children and adolescents (37 boys, 13 girls) aged between 5-18 years suffering from atopic bronchial asthma. The mean age of 50 children was 11.2 ± 0.4 years. The test group completed a course of speleotherapy in the Nakhchivan Physiotherapy Center "Duzdag Magara". The study also included a comparison group consisting of 30 children with asthma who received only drug treatment (basis therapy) and the control group, which included 10 healthy children without allergic diseases and with a negative history of allergy.

The selection criteria for the test group were the presence of an established diagnosis of atopic bronchial asthma and the absence of its exacerbation for the period of treatment. The study included children diagnosed with mild and moderate persistent asthma. The age of disease onset was 5.0 ± 0.2; the method of the treatment was 15 procedures per day.

Speleotherapy Regimen

Speleotherapy was carried out in the post-attack period under the following scheme: adaptation - main regimen - re-adaptation. The adaptation regimen was conducted during the first 2 days during daylight hours and the underground section stayed according to the following scheme: 4 hours - for children over 10 years and 1.5-2 hours – for children from 5 to 10 years.

The main regimen included a day stay in the speleo section. Children between 5 and 10 years of age were given a 4-hour day sleep in a salt cave. Children over the age of 10 were allowed to sleep in a salt cave for 8-9 hours at night. The re-adaptation regimen included 2 hours for children between 5-10 years, a 4-hour day stay for over the age of 10 years in caves in the last 2 days of treatment and that allowed us to avoid the risk of withdrawal syndrome.

Lung Function Studies

Lung function was evaluated by determining the spirometric indices, such as forced vital capacity (FVC), forced expiratory

Table 1. Subgroup analyses of the effect of speleotherapy on pulmonary function.

Parameters (%)	pre-treatment and post-treatment values	Patients Groups			
		Group I (n=23)	p value	Group II (n=27)	p value
FVC	pre-treatment values	83.3 ± 1.6	p<0 .01	80.5 ± 1.5	p<0 .01
	post-treatment values	100.5 ± 2.6		97.0 ± 1.9	
FEV1	pre-treatment values	70.9 ± 1.6	p<0 .01	67.6 ± 1.2	p<0 .01
	post-treatment values	96.7 ± 2.1		88.4 ± 2.2	
FEV1/FVC	pre-treatment values	92.9 ± 1.8	p<0 .05	76.0 ± 1.2	p<0 .01
	post-treatment values	77.2 ± 6.1		90.7 ± 1.3	
FEF	pre-treatment values	61.0 ± 4.0	p<0 .01	51.0 ± 1.6	p<0 .01
	post-treatment values	79.7 ± 3.6		77.4 ± 2.5	
PEF	pre-treatment values	70.0 ± 2.0	p<0 .01	65.1 ± 1.2	p<0 .01
	post-treatment values	83.1 ± 2.6		80. 9± 2.9	

Abbreviations: FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; FEV1/FVC: forced expiratory volume in 1 sec as a percentage of FVC; FEF: forced expired flow at 25–75%; PEF: Peak expiratory flow.

Values are shown as mean ± standard deviation. Group I - children with mild asthma; Group II - children with moderate persistent asthma

volume in the first second (FEV1), forced expiratory volume in the first second as a percentage of FVC (FEV1/ FVC %), forced expired flow at 25–75% of FVC (FEF 25-75%), peak expiratory flow (PEF). Spirometric values were evaluated with the standard values and the results were expressed in percentages.

Measurement of Fractional Exhaled Nitric Oxide (FeNO)

FeNO is an endogenous gas that can be measured in a human breath test in the presence of airway inflammation. The determination of the marker of airway inflammation, FeNO was carried out by using the non-invasive and portable analyzer; NIOX MINO (Aerocrine AB, Solna, Sweden).

Analysis of Serum Cytokine

The laboratory examination of patients included the study of Interleukin (IL)-5, IL-13, and Interferon-gamma (IFN-γ) in the serum by enzyme-linked immunosorbent assay (ELISA).

Statistical Analyses

Statistical processing of the obtained results was carried out using the non-parametric pairing criterion W-Wilcoxon-a in the Statistical Package SPSS-26. Intergroup comparisons were carried out using the Mann-Whitney U test, and intra-group comparisons were carried out in MS Excel-2000 and SPSS-26 with Wilcoxon criteria. $p<0.05$ was accepted as significant.

RESULTS

The effect of speleotherapy on the amount (volume) and speed (flow) of air that was inhaled or exhaled from the lungs was carried out by dynamic control before and after speleo treatment. At the end of the speleotherapy, patients showed positive changes in the values of lung function.

In asthmatic children with a mild form of bronchial asthma, after a treatment of speleotherapy, FVC was improved significantly from 81.3 ± 1.6% to 100.5 ± 2.6% ($p<0.01$), FEV1 was improved and reached from 70.9 ± 1.6% to 96.7 ± 2.1 ($p<0.01$), FEV1/FVC was increased from 78.9 ± 1.5% to 92.9 ± 1.8% ($p<0.05$), FEF 25-75% was changed from 61.0 ± 4.0% to 79.7 ± 3.6% ($p<0.01$), and finally PEF was increased from 70.0 ± 2.0% to 83.1 ± 2.6% ($p<0.01$) (Table 1). Changes were found only in patients with mild asthma receiving only basic treatment: FVC from 82.4 ± 1.6% to 89.7 ± 2.2% ($p=0.005$), FEV1 from 67.9 ± 1.7% to 79.7 ± 1.7% ($p=0.003$), FEV1/FVC from 77.0 ± 2.1% to 85.0 ± 2.0% ($p=0.003$), FEF from 25-75% 55.5 ± 2.5% to 67.5 ± 3.6% ($p=0.005$), PEF from 70.0 ± 2.0% to 83.1 ± 2.6% ($p<0.001$).

In children with moderate persistent bronchial asthma, positive changes were also observed in lung function after the treatment of speleotherapy. These patients had increased their VC on average by 20.5% (pretreatment value: 80.5 ± 1.5%, posttreatment value: 97.0 ± 1.9%, $p<0.001$), FEV1 by 30.8% (pretreatment value: 67.6 ± 5.2%, posttreatment value: 88.4 ± 7.5%, $p<0.01$), FEV1/VC by 19.8% (pretreatment value: 76.0 ± 1.2%, posttreatment value: 90.7 ± 1.3%, $p<0.01$), FEF 25-75% by 51.7% (pretreatment value: 51.0 ± 1.6%, posttreatment value: 77.4 ± 2.5%, $p<0.01$), PEF by 24.3% (pretreatment value: 65.1 ± 1.2%, posttreatment value: 80.9 ± 2.9%, $p<0.01$). The results show an improvement in bronchial passage at the small, medium, and large bronchi. The indicators of the main treatment group changed as follows: FVC (pretreatment value: 80.9 ± 1.1%, posttreatment value: 89.1 ± 1.9%, $p<0.001$), FEV1 (pretreatment value: 64.0 ± 1.5%, posttreatment value: 77.9 ± 1.5%, $p<0.001$), FEV1/VC by (pretreatment value: 76.1 ± 1.2%, posttreatment value: 82.1 ± 4.4%, $p=0.012$), FEF 25-75% (pretreatment value: 52.5 ± 2.3%, posttreatment value: 64.7 ± 2.5%, $p<0.001$), PEF (pretreatment value: 65.8 ± 1.2%, posttreatment value: 76.3 ± 2.0%, $p<0.001$). In both groups, a positive dynamic change in spirometric indicators was observed. In the group where speleotherapy was performed, the increase in indicators was more significant than the other group.

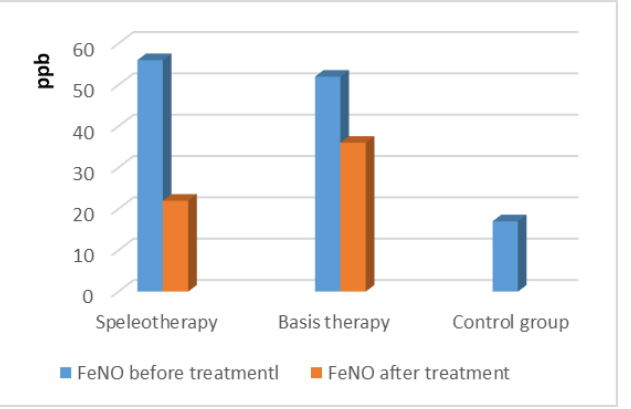

Figure 1. Nitric oxide levels in the exhaled air in children with mild persistent atopic bronchial asthma

Abbreviations: FeNO: Fractional exhaled nitric oxide

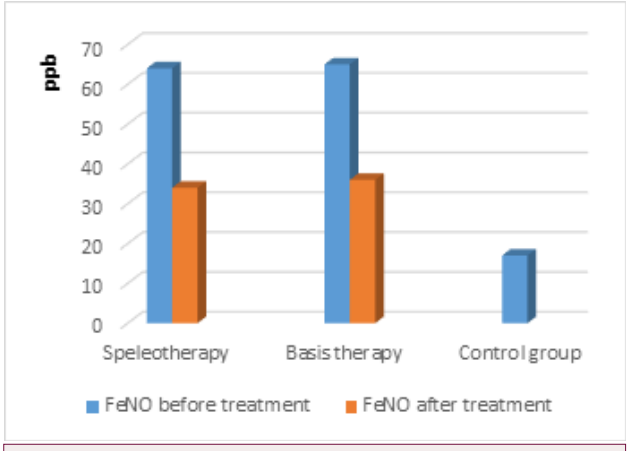

Figure 2. Nitric oxide levels in the exhaled air in children with persistent atopic bronchial asthma of moderate severity

Abbreviations: FeNO: Fractional exhaled nitric oxide

The effectiveness of speleotherapy was evaluated by measurement of FeNO. Prior to treatment, the level of FeNO in all patients, even with a mild form of the disease, was significantly increased compared to the healthy group (17.9 ± 2.4 ppb; p=0.001). Thus, the level of nitric oxide in the exhaled air of patients with a mild course receiving basic therapy was 52.8 ± 4 ppb (p<0.001), in the moderate course of the disease was 65.8 ± 4.6 ppb (p<0.001). In patients with mild disease that undergo complex treatment, the level of FeNO in the exhaled air was 56.9 ± 5.6 ppb (p<0.001) and was 64.0 ± 3.1 ppb (p<0.001) in case of moderate asthma (Figure 1). An increase in the amount of nitric oxide in the exhaled air confirmed the presence of persistent allergic inflammation in the respiratory tract (Figure 2).

The level of FeNO in the exhaled air of patients receiving only basic treatment after treatment was 36.5 ± 2.5 ppb (p=0.003) in a mild form of the disease and 44.0 ± 4.5 ppb (p<0.001) in a moderate form of the disease.

After 4 weeks of treatment, the patients showed a significant positive change in the level of FeNO, which was 22.2 ± 2.2 ppb (p<0.001) and 34.3 ± 33.2 ppb (p<0.001), respectively, reflecting the improvement of the clinical performance against the background of speleotherapy. After 4 weeks, in patients who received speleotherapy, the level of FeNO was decreased by 2.6 times in mild form and 1.9 times in moderate form, against the background of basic treatment, these indicators were decreased by 1.4 and 1.5 times, respectively.

The level of nitric oxide in exhaled air was significantly reduced in patients with speleotherapy compared to the group receiving only basic treatment.

Thus, the obtained results suggest that the level of FeNO varies depending on the severity of the disease and the method of treatment. The level of nitric oxide in respiration, which is the main biomarker of eosinophilic allergic inflammation, decreased more significantly in patients with speleotherapy compared to the group receiving only basic treatment. This, in turn, gives a reason to consider a greater decrease in persistent allergic inflammation in the respiratory tract after speleotherapy.

In the remission period of the disease, in the absence of clinical symptoms, the effectiveness of speleotherapy was evaluated based on the dynamics of cytokine status indicators in our study. Analysis of the results of the cytokine study revealed a regular increase in Th2-like cytokines in patients receiving speleotherapy, depending on the severity of bronchial asthma.

In the group that received only basic treatment for the mild forms of the disease, IL-5 was 7.50 ± 1.12 pg/mL, (p=0.002), IL-13 was 7.38 ± 1.29 pg/mL (p=0.001), and IFN-γ was 3.30 ± 0.97 pg/mL (p=0.019). In the serum of children with mild disease, the level of IL-5 before speleotherapy treatment was 6.52 ± 0.59 pg/mL (p=0.008), with moderate asthma 8.24 ± 1.25 pg/mL (p=0.063). A similar positive improvement was observed for IL-13, whose average serum level before treatment was 5.82 ± 2.54 pg/mL (p=0.063) for mild asthma and 10.41 ± 3.44 pg/mL (p<0.001) for moderate asthma (p=0.094). As the severity of the disease worsened, the level of IFN-γ in the serum of patients decreased and was 2.44 ± 0.52 pg/mL (p=0.002) with mild asthma, with moderate asthma 1.81 ± 0.28 pg/mL (p<0.001).

After a course of speleotherapy treatment in children with mild atopic bronchial asthma, the level of IL-5 in the blood serum decreased to 4.37 ± 0.12 pg/mL (p=0.008). The IL-13 level after treatment also decreased to 1.44 ± 0.26 pg/mL (p=0.038). The IFN-γ level after treatment increased to 6.87 ± 0.93 pg/mL (p=0.008) (Figure 3). In the group where basic treatment was carried out for a mild form of the disease, IL-5 was 5.64 ± 0.49 pg/mL (p=0.225) IL-13 was 2.89±0.61 pg/mL (p=0.043), and IFN-γ was 4.80 ± 15 pg/mL (p=0.138).

In patients who received only basic treatment, with a moderate form, IL-5 decreased from 8.50 ± 2.02 pg/mL to 5.60 pg/mL (p=0.225), (decreased 1.4 times), IL-13 was 6.79 ± 2.12 pg/mL to 3.59 ± 0.98 pg/mL (p=0.063), (decreased by 1.8 times), IFN-γ decreased to 1.73; it increased from 0.24 pg/mL to 4.17 ± 0.97 pg/mL (p=0.128).

In the group of children with moderate asthma, the dynamics of the cytokines after the treatment of speleotherapy were the following. IL-5 level in blood serum decreased to 5.05 ± 0.2 pg/mL (p=0.001). The level of IL-13 after treatment decreased by

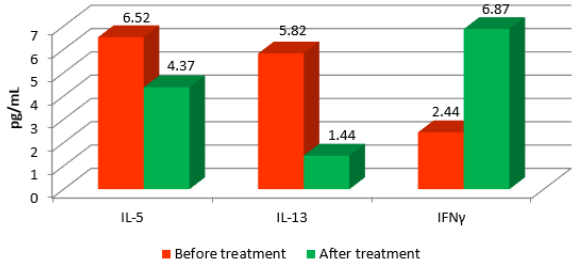

Figure 3. Cytokine indices in the mild course of bronchial asthma in the dynamics of speleotherapy.

Abbreviations: IL-5: Interleukin 5, IL-13: Interleukin 13, IFN-γ: Interferon-gamma

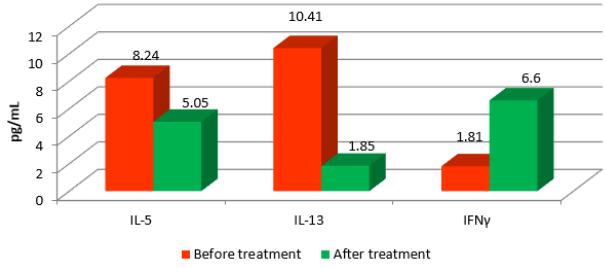

Figure 4. Indicators of cytokines in the medium-heavy bronchial asthma current in the cave therapy dynamics.

Abbreviations: IL-5: Interleukin 5, IL-13: Interleukin 13, IFN-γ: Interferon-gamma

5.6 times and was 1.85 ± 0.65 pg/mL (p=0.001). IFN-γ level after treatment increased by 3.6 times and became 6.60 ± 1.00 pg/mL (p<0.001) (Figure 4).

Thus, during the study of the cytokine profile of patients with atopic bronchial asthma in various variants of treatment, significant changes in the level of Th1 and Th2 cytokines were observed. In patients receiving speleotherapy, these changes have become more significant.

DISCUSSION

As a result of the study, the following was revealed. Before treatment, in all patients, even those with a mild form of the disease, the level of FeNO increased significantly compared to the healthy control group. In patients receiving basic treatment, the levels of FeNO in the exhaled air, hence an eosinophilic allergic inflammation, decreased after treatment compared to the state before treatment (p <0.001). The levels of FeNO in the exhaled air of patients with a mild and moderate form of the disease who received complex treatment with speleotherapy were decreased. After a 4-week course of treatment in patients who received speleotherapy, the level of FeNO in mild and moderate forms of asthma was decreased by 2.6 times and by 1.9 times respectively; against the background of basic treatment, these indicators decreased by 1.4 and 1.5 times, respectively (12).

Studies have shown a naturally positive effect of speleotherapy on cytokine parameters in children with mild and moderate atopic bronchial asthma after complex treatment compared to patients who received only basic treatment (13, 14). Assessment of pulmonary functions also showed improvements in patients after speleotherapy compared to the control group (15).

The "Duzdag Therapeutic Center" is a physiotherapeutic center with salt caves located in Nakhchivan Azerbaijan at an altitude of 1173 meters above sea level. The recreation center is an underground cavern hospital, providing conditions for optimal treatment and health measures. It is a center where atopic asthma and other chronic respiratory diseases are treated. The unique chemical composition of Duzdag salt that doesn't have analogs is: NaCl: 98.4% (highly dispersed aerosol), $MgCl_2$: 0.06%, $CaCl_2$: 0.04% (8).

Our study results revealed that remission of the disease depends on the severity which was observed in 70-80% of our patients and ranged from 6 months to 1-1.5 years due to the speleotherapy. As a method of medical rehabilitation for patients with bronchial asthma, speleotherapy leads to a decrease in the number of attacks, reduces the use of bronchodilators, and improves the indicators of the function of external respiration. The appointment of a course of speleotherapy for children with bronchial asthma according to an adapted scheme is of great practical importance since it may be useful in the treatment of the disease.

Ethics Committee Approval: The study was approved by the Ethics Committee (Protocol No: 28) of Azerbaijan Medical University.

Informed Consent: Parents signed a consent form for their children to participate in this study.

Peer-review: Externally peer-reviewed.

Authors' Contributions: Conception/ design of Study- L.A.; Data acquisition: N.E.; Data Analysis/Interpretation: A.K.; Drafting Manuscript: L.A., A.K.; Critical Revision of Manuscript: N.E.; Final Approval and Accountability: L.A., N.E., A.K.

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