
Rehabilitation of Allergic Diseases in Children — Climatothermalsotherapy as a Power Tool in Achieving Optimal Disease Control

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Additional information is available at the end of the chapter

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1. Introduction

Incidence of allergic diseases is overall increasing in last few decades. This increase is especially outlined in pediatric population. In European Union prevalence is between 2-11% [1]. Rehabilitation of allergic diseases, primarily asthma or recurrent obstructive bronchitis is a powerful mechanism to achieve better control of the disease which is not sufficiently used for this purpose. The cost of treating asthma takes fifth place in health systems since they are accumulated over a lifetime. Direct costs go for medications and hospitalization costs, and indirect in terms of loss of working and school days.

Since ancient times it has been known that spending time by the sea has a beneficial effect on the respiratory system, and in recent years this fact is making a strong “come back”. The rehabilitation program of this sort usually lasts from two to three weeks, which in combination with a specific climate leads to the effect that allows better control of asthma and other allergic diseases. The medical rehabilitation program usually consists of sterilized and nebulised sea inhalation, inhalation of nebulised essential oils and breathing exercises [2]. It is available in a few european centers till this day to our knowledge, our institution being one of those centers.

The favorable location of our institution in the most peaceful part of the Croatian littoral is protected from strong winds from the north thanks to the adjacent mountain slopes and from the south thanks to the island of Krk, providing a mild and relaxing climate. This region's characteristic climate features are its dry, bright and pleasantly warm summers and mild winters, with a healthy, local system of winds.

The difference between the average annual maximum and minimum temperatures is small, whilst the difference between day and night temperatures is moderate and the total number of hours of sunshine throughout the year is 2,500. Over the last 100 years, the average temperature during the winter has been 14,2°C whilst the average summer temperature is 23,6°C. Snow, fog and temperatures lower than 5°C are very rare. The sea temperature during the summer is almost 27°C.

The sea air distinguishes itself by its purity and abundance of healthy oligominerals, its natural sea salt aerosols, ozone and essential pine, lavender and macchia oils, with no noxious pollen allergens (especially pollen) and waste gases.

The particularities and advantages in treatment is the implementation of climatic therapy and thalassotherapy is the application of the physical, chemical, natural and healthcare factors inherent to the sea and the coast that are the sea air, and climate together with the seawater [2].

2. Climatic therapy

The medicinal benefits of the coastal climate emerge from the extremely favorable geographic region in which is our institution located. Institution's favorable position brings about a mild and relaxing climate. Climate therapy and the implementation of natural medical factors performed by means of a free approach to the user or by medically conducted therapeutic procedures. This free approach consists of residing in situ, with walks and other forms of outdoor physical activities, close to the sea. Therapeutic procedures also consist of breathing exercises and other physical procedures and exercises that are performed outdoors and by the sea, under the supervision of a physical therapist.

3. Thalassotherapy

Using thalassotherapy procedures for medical purposes primarily means using seawater during therapeutical procedures, and in our institution there is a variety of ways of inhaling seawater as well as different procedures of physical medicine and rehabilitation performed in the sea.

Seas and oceans have always magically attracted people. The ancient Egyptians, Greeks and Romans considered medicinal baths as important as medical treatments. Thalassotherapy implies the complete treatment of the body and mind based on an ancient belief in the natural healing, both physical and chemical, properties of seawater. This term comes from the Greek words „thalassos“ that means sea and „therapeia“ that means therapy. Today the term „theraphy from the sea“ considers natural and alternative treatments for healing a variety of diseases, accompanied by conventional methods of therapy and rehabilitation for a variety of diseases and states, antiaging treatments as well as techniques aimed at relaxation and reducing stress [2].

4. Inhalation therapy

The therapeutic value of seawater is determined by its physical and chemical characteristics. The medicinal properties of the sea have been known since ancient times. The Adriatic Sea is considered to be the cleanest among all the Mediterranean seas. Its seawater is nothing more than a solution of minerals: sodium, magnesium, calcium, chloride, sulphate and bicarbonate. As well as this, it contains and trace elements: copper, manganese, selenium and zinc. Papers have confirmed that the salts and microelements (Ca, Fe, Mg, Na, Cu, Sn and other) contained in the seawater have an antiseptic, antibacterial and antiviral effect.

Inhalation therapy is performed in a specialized Inhalation center, which is unique not only on the entire Adriatic area, but also in Europe. Modern devices for inhalation therapy enable the exceptional quality of the dispersion of both the natural features of the seawater and essential oils and medications, thus achieving the excellent results of inhalation therapy.

Inhalation therapy involves the introduction of dispersed natural healing solutions or medications of gaseous substances locally into the respiratory system and subsequently through the lung tissue partially into the systemic circulation. A therapeutic agent together with the help of modern technology is heated to the temperature of the human body and then disperses in aerosol particles of different sizes. For example, aerosol particles up to 5 microns (dry inhalation) are intended for the lower respiratory tract, while aerosol particles of 5-10 microns (wet inhalations) are intended for the upper respiratory tract. Considering the unique system of both the upper and lower respiratory tracts and the fact that 8 out of 10 patients with asthma also suffer from allergic rhinitis, both types of inhalation are applied depending on the indication.

Among other inhalants, inhalations of essential oils are used as well as inhalations of medications (corticosteroids, mucolytics, Beta2-agonists, anticholinergic). For obstructive pulmonary disorders IPPB inhalers i.e. intermittent positive pressure breathing are used.

The use of inhalation therapy of essential oils for medical purposes today is confirmed by numerous scientific researchers. Essential oils for inhalation have been applied since 1961 on the recommendation of Ivo Padovan, M.D., and the formula has remained unchanged.

The nebulised essential oil is composed of:

Phenolum liquefactum – a mixture of phenol with camphor and menthol, that acts locally anaesthetically, with a bacteriostatic effect.

Mentholum – in nature mint, which contains essential oils with mint, it is widely used in traditional medicine.

Camphora – camphor is obtained from the distillation process of essential oils of the cinnamomum camphora tree – kamforaceae; it has a positive effect on the circulation of blood vessels as well as respiration in asthma patients.

Aetherolum terebintinae – oil which is obtained from pine wood resin in a variety of ways, the main ingredients are terpenes.

Aeterolum eucalypti – is obtained from the distillation of eucalyptus leaves, this oil was once used as a medicaton against malaria whilst today it is used for treating disorders like pertussis and COPD.

The rehabilitation of the lower respiratory organs is performed by specialists in paediatrics and paediatric pulmonology with the support of ENT specialists, specialists in dermatology, physical medicine and rehabilitation as well as of physiotherapists and accompanying medical staff.

Above mentioned inhalations are applied in acute, subacute and chronic conditions as well as allergic upper and lower airway inflammation such as asthma and allergic rhinitis. Reconvalescents from pneumonia and influenza, chronic obstructive pulmonary disease patients as well as preoperative and postoperative treatment of respiratory surgical patients.

The purpose of above mentioned inhalation therapy is breaking the pathophysiology chain events that originated from inflammation as basic process. Hypersecretion and eosinophilic or neutrophilic infiltration leads to eventual deterioration and functional failure of the respiratory mucosa. However, thanks to the enormous regenerative capacity of respiratory mucosa, intensive respiratory rehabilitation is able to bring it closer to a more or less normal state [3].

It is common that each inhalation procedure is preceded by accurate diagnosis, status of the inflammatory process as well as localization using multidisciplinary approach and diagnostic tools such as spirometry and fraction of exhaled nitric oxide (FeNO). It is widely known that the upper part of respiratory tract is associated with the lower part of the respiratory tract in terms of pathophysiology. Therefore, respiratory mucosa is unique in terms of reactions and pathophysiological mechanisms. Pathological events in respiratory system must be approached multidisciplinary as teamwork of otorhinolaryngologist and pediatric allergologist or pediatric pulmonologist.

The fastest and most effective application of therapeutic substances is if and when possible local application in terms of direct contact with diseased tissue. However, inhalation therapy with local action has also general action due to absorbtion and penetration of therapeutic substances through lung tissue, with a total area of 120 m². It is calculated that there is about 75 billion alveoli, which are shrouded in capillaries with walls that are approximately 0.8 microns thick, being the thinnest of all the capillaries in the body.

Inhalation therapy itself should be preceded by preinhalation procedure where the diseased mucosa is prepared as much as possible to receive the therapeutic substances. Preinhalation procedure is done by cleaning the pathological secretions, krust and pus by aspiration, flushing, gurgling and humidification. After accurately diagnosed localization and severity of the disease process, it is also important to choose size of the particles, as well as type of application.

If the problem is localized in upper respiratory tract, particle size should be from 7-15 microns, the middle part of the respiratory tract (trachea and bronchi) 2-5 microns, and the lower part of 0.5-1 microns.

To make the rehabilitation process (inhalations and climate factor) more objective, we chose to use FeNO as diagnostic tool by measuring its value at start and finish of rehabilitation process.

The fraction of exhaled nitric oxide (FeNO) is used as a biomarker for diagnosing and monitoring respiratory allergies, or as an indicator of successful treatment of asthma in adults and children. The measurement of exhalation is quick and simple test that can detect the inflammation before the symptoms become proportional to the actual degree of eosinophilic inflammation in the respiratory system. The largest portion of the nitric oxide (NO) is formed under the influence of inducible NO synthase respiratory mucosa [4,5,6]. It has a diagnostic role and a role in monitoring the effectiveness of the treatment. Measurement of FeNO began in mid-'90s and since 2005 it is recommended by the European Respiratory Society and the American Thoracic Society as a relevant diagnostic method of proving and monitoring asthma [7,8,9]. There's more than one kind of measuring device, and in our institution CLD 88 Analyzer was used in this research. With adequate antiasthmatic therapy in the treatment of children suffering from asthma, its place also has climatothermal therapy rehabilitation process that takes place in our institution. Since the times of Hippocrates, who talks about benefits of the coastal and sea environment, and Galen, who recommended breathing the air that breaks on the rocks by the sea (later known as aerosol), patients with respiratory problems seek relief in such environment. Our hospital in today's form itself has tradition that lasts over 50 years in treating such diseases. Climatic factors, marine aerosol and absence of pollution are the main principles of climatothermal therapy. The rehabilitation process in our institution consists of inhalation therapy and breathing exercises, as well as appropriate corrective exercises for chest and posture, hydrokinesiotherapy and physical procedures drainage administered by the inhalation of dry and moist marine aerosol and nebulised essential oils. Rehabilitation treatment usually lasts 14 or 21 days. The aim of this study was to determine the favorable impact of climatothermal therapy rehabilitation process in our institution by measuring FeNO at the beginning and end of treatment, and its dynamics.

5. Patients

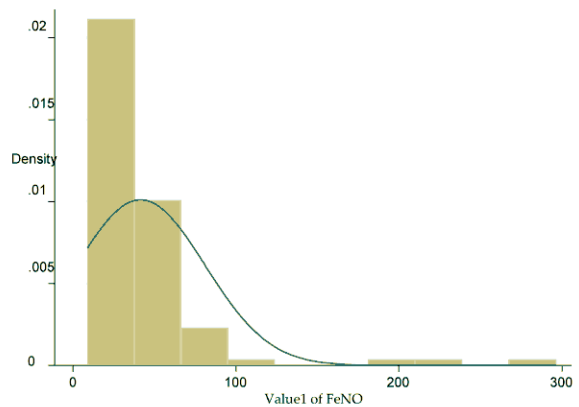
We tested 107 children (up to 18 years of age) who were treated during 2014 with climatothermal therapy rehabilitation program using inhalation of nebulised sea water, inhalations of nebulised essential oils and breathing exercises. The duration of the rehabilitation program was 14 or 21 days. In addition to sociodemographic data, we examined the value of FeNO on arrival and on departure after completion of rehabilitation treatment.

6. Methods

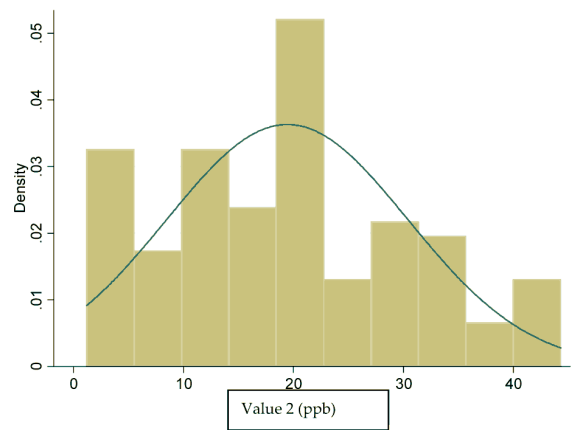
In the initial part of calculating results classical methods of descriptive statistics were used. First we calculated numeric indicators of central tendency and dispersion of variables FeNO

on arrival and on departure. Shapiro-Wilks test showed that variable FeNO was not normally distributed (graphs 1 and 2) on arrival ($p < 0.001$) nor on departure ($p = 0.016$) and further statistical analysis was based on nonparametric approach. The difference in indicators of central tendency between groups was also tested, we used the Mann-Whitney test, and for comparison of paired data Wilcoxon test. Testing the difference in the proportion is based on the z-test.

Graphical comparison of data is based on the creation of Boxplot chart. Statistical data were calculated using program Statistica 9,0 software



Graph 1. The normality distribution analysis of the the variable "FeNO on arrival"



Graph 2. The normality distribution analysis of the variable "FeNO on departure"

7. Results

In this paper the main variables of interest were FeNO on arrival and departure.

The basic numerical indicators for these two variables are shown in the following table:

variable	mean	p50	sdiqr	cv	range
value~1	41.48411	30.5	19.4	25 .9507657	287.4
value~2	19.43551	19.4	10.98513	16.3 .5652091	43.1

Table 1. FeNO on arrival (value1) and departure (value2)

Note that the coefficient of variation (CV) for both variables is greater than 0.5, which tells us that there was present a significant dispersion when measuring and that median is the better indicator of central tendency than the arithmetic mean, which supports the selected nonparametric methods. It is important to note the extremely large range of measured data with variable FeNO at arrival.

First, we wanted to check whether there is a difference in the measurement of FeNO on arrival and departure. We confirmed our hypothesis that FeNO on departure is markedly lower than FeNO on arrival at an extremely high level of significance ($p < 0.001$). In other words, the median value of the sample fell for 11 units, and the data for FeNO on departure are far more homogeneous, which means that the coefficient of variation was reduced by almost 50%.

Comparison of FeNO on arrival and departure is shown in the figure below:

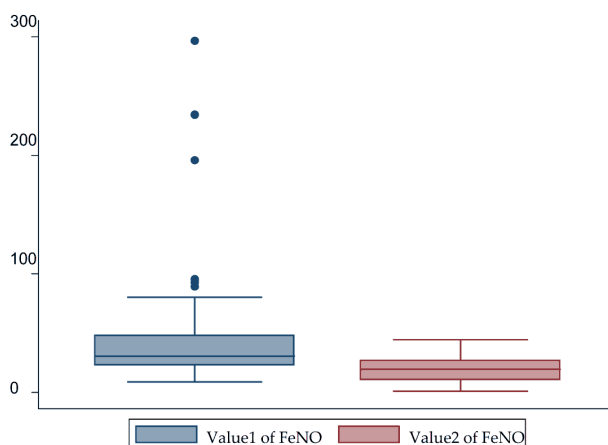


Figure 1. FeNO on arrival (value1) and departure (value2)

Now we wanted to check whether children who were 21 days in the treatment have lower output FeNO compared to those who had a stay of 14 days. The assumed hypothesis has been accepted because the Mann-Whitney test showed that there was a statistically significant difference at a weak level of significance ($p=0.0971$) in the median values between groups.

Tabular and graphical representation are given below:

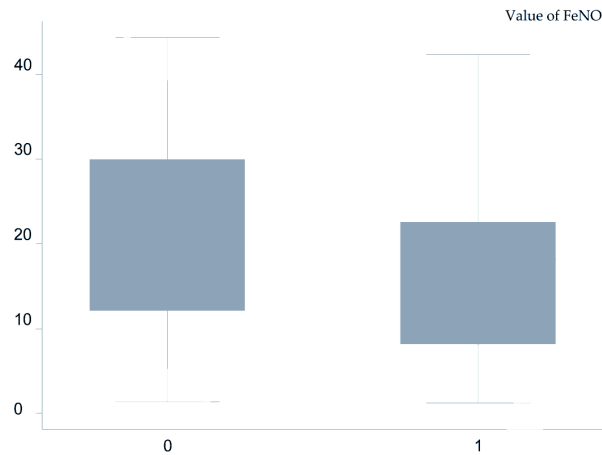


Figure 2. FeNO value on 21 days and 14 days of therapy total

Duration21(1)/14(0)	mean	p50	sdiqr	cv	range
0	21.22745	20.1	10.60664	17.8 .4996663	42.9
1	17.80357	18.15	11.16276	14.35 .6269957	41.1

Table 2. FeNO value on 21 days and 14 days of therapy total

Finally, we wanted to examine whether children with positive SPT(skin prick test) test have higher average FeNO on arrival or on departure. Positive SPT test being the test that is positive with at least one or more inhalatory allergens.

For values of arrival data are displayed in the following table and graph:

SPT 1/0	mean	p50	sdiqr	cv	range	min
0	31.98605	29.3	16.56739	22 .5179568	83.4	9.3
1	47.86563	36 48.28566	26.75	1.008775	287.4	8.9
total	41.48411	30.5	39.44167	25 .9507657	287.4	8.9

Table 3. SPT test (1 positive/0 negative) and FeNO on arrival

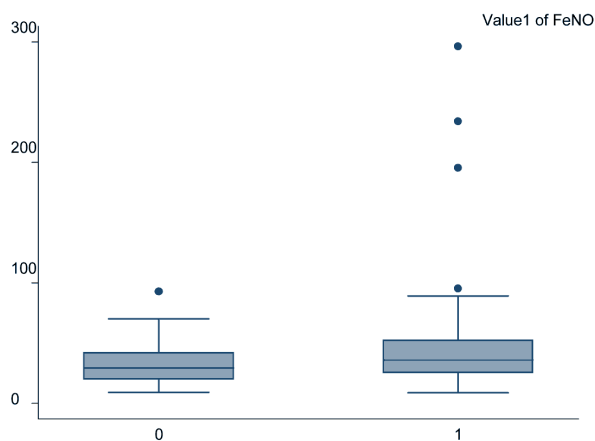


Figure 3. SPT test (1 positive/0 negative) and FeNO on arrival

The difference in the median values of Mann-Whitney test was significant ($p=0.0383$), which is not the case when patients were leaving ($p=0.3618$).

Indicators for this case are given below:

SPT 1/0	mean	p50	sdiqr	cv	range	min
0	18.14419	19.1	9.591422	11.4 .5286224	38.1	2.1
1	20.30313	20	11.82388	19.8 .5823674	43.1	1.2

Table 4. SPT test (1 positive/0 negative) and FeNO on departure

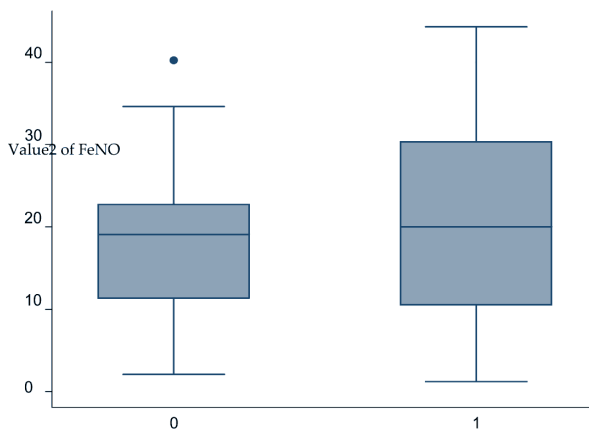


Figure 4. SPT test (1 positive/0 negative) and FeNO on departure

8. Discussion

Specific climate has a positive effect on allergic respiratory system diseases, but there are not many studies that objectively prove this claim. There is also a problem of multicentric studies since there is not many centers that provide this kind of medical treatment as well as no standardised procedures within these centers. In our institution climatothermalasso therapy rehabilitation program is carried out while taking permanent antiasthmatic therapy if there is one at arrival.

The rehabilitation program lasts two to three weeks, which in combination with a specific climate leads to the effect that enables better asthma control. In our analysis, we followed the FeNO as a biomarker of inflammation at the beginning and the end of the treatment. With statistically relevant significance it can be established that climate has a positive effect on reducing the values in FeNO as a biomarker of inflammation and thus favorably affect on asthma control. Kaminski et al in their study had similar observations [10]. Of course, it should be taken into account that specific micro factors like air pollution as well as the number and proximity of roads and clean air and seawater [11,12]. Those parameters are evaluated several times a year. Also, we should not neglect the fact that the permanent antiasthmatic therapy at our institution is taken regularly ensuring good compliance. Furthermore, close supervision by medical staff ensures the cooperation of patients, which can affect the final result, this segment is provided. Furthermore, there is a question if accumulated effect of climatothermalasso therapy reduces the need for acute hospitalizations, as well as increased dosage of inhaled corticosteroids. There is an indication of positive answer on this question provided by study taken in ten year period following the group of 143 children who were treated over ten years in our institution, it was stated that children who were five or more times treated with climatothermalasso therapy rehabilitation treatment for a period of three weeks, were using significantly less inhaled corticosteroids and they had statistically significant less asthma exacerbations compared to the control group that did not use climatothermalasso therapy at all [13]. However, there is a need for further research in this area.

We find that FeNO as a diagnostic tool is excellent, reproducible and non-invasive method of evaluation or reevaluation, which gives us an insight into the success of therapeutic methods and can guide us in tailoring therapy in terms of individual approach to each patient with asthma.

9. Conclusion

Besides usual antiasthmatic therapy in the treatment of asthmatic children, there is an important place for climatothermalasso therapy rehabilitation program. We can say that climatothermalasso therapy rehabilitation process in observed patients has a positive effect on reducing the FeNO values and asthma control. There is a need for further research on impact of cumulative therapy in patients with multiple treatments in our institution on a larger number of patients. Importance of good communication among physicians who regularly control

patients treated in their residential place and the doctors who observe patients during climatothermal therapy rehabilitation process in our institution with the aim of better control of the underlying disease, should be emphasized.

Climatothermal therapy is a powerful tool in achieving optimal allergic disease control that is not enough incorporated in algorithms of allergic disease management. It should be used on regular basis in order to reduce dosage of medications and reduce number of exacerbations of disease, therefore, in cutting down the expenses of health system and providing better quality of life for those patients.

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