LETTER TO THE EDITOR

EFFECTIVENESS OF ISCHIA THERMAL WATER NASAL AEROSOL IN CHILDREN WITH SEASONAL ALLERGIC RHINITIS: A RANDOMIZED AND CONTROLLED STUDY

M. MIRAGLIA DEL GIUDICE[1], F. DECIMO[1], N. MAIELLO[1], S. LEONARDI[2], G. PARISI[3], M. GOLLUCCIO[2], M. CAPASSO[1], U. BALESTRIERI[1], A. ROCCO[1], L. PERRONE[1] and G. CIPRANDI[4]

[1]Pediatric Department "F.Fede", II University of Naples, Naples; [2]Pediatric Department, University of Catania; [3]UOC Pediatrics and Neonatology, ASL Na-2, PO "Anna Rizzoli", Lacco Ameno; [4]Azienda Ospedaliera Universitaria San Martino, Genova, Italy

Received April 14, 2011 – Accepted October 10, 2011

Allergic rhinitis is characterized by local inflammation. Nasal lavage may be a useful treatment, however, there are few studies on this topic. This study aims to evaluate the effects of Ischia thermal water nasal irrigation on allergic rhinitis symptoms and airway inflammation during the period of natural exposure to *Parietaria* pollen in children with allergic rhinitis and intermittent asthma. Forty allergic children were randomly divided into two groups: the first group (Group 1) practiced crenotherapy with thermal water aerosol for 15 days per month, for three consecutive months, the control group (Group 2) was treated with 0.9% NaCl (isotonic) solution. In addition, all children were treated with cetirizine (0.5 gtt./kg/day once daily). Nasal symptom assessment, including Total Symptom Score (TSS), spirometry, and exhaled nitric oxide (FeNO) were considered before the treatment (T0), at the end of the treatment (T1) and again 2 weeks after the end of the treatment (T2). The study was registered in the Clinical Trials.gov (NCT01326247). Thermal water significantly reduced both TSS and FeNO levels and there was a significant relationship between reduction of nasal symptoms and FeNO values at the end of treatment with thermal water. In conclusion, this study shows that nasal crenotherapy with the hyper-mineral chloride-sodium water of Ischia was effective in children with seasonal allergic rhinitis based on the sensitivity to Parietaria. These results demonstrate that this natural treatment may be effective in a common and debilitating disease such as the allergic rhinitis.

The burden of allergic diseases is continuously increasing in all industrialized countries and allergic rhinitis can lead to a substantial deterioration in children's quality of life with relevant effects on learning and friendship (1). Nasal obstruction is a main symptom and is closely dependent on allergic inflammation (2). Thus, anti-inflammatory drugs, mainly topical corticosteroids, are frequently used for treating allergic rhinitis. However, topical drugs may be scarcely effective if nasal secretions are not sufficiently removed by nasal lavage. Recent studies have shown that nasal irrigation with hypertonic solution was able to determine a significant improvement in rhinitis symptoms in children

Key words: thermal water, nasal lavage, Ischia, allergic rhinitis, children

Mailing address: Giorgio Ciprandi, M.D.
Semeiotica e Metodologia Medica I,
Viale Benedetto XV 6,
16132 Genoa, Italy
Tel: ++39 10 35331820
Fax: ++39 10 3538664
e-mail: gio.cip@libero.it

0394-6320 (2011)

allergic to pollen and to reduce the antihistamine consumption during the pollination period (3-4). A significant reduction in levels of specific IgE to pollen (*Dactylis glomerata*), during the pollination season, by daily sodium chloride nasal-sinus irrigation, was also reported as a consequence of the reduced permanence of the allergen on the nasal mucosal tissue (4). Another study has shown that saline solution irrigations of the nasal cavities reduced the nasal mucosa allergic inflammation by significantly decreasing the levels of interleukin-8 (5).

It is well known that allergic rhinitis is often associated with asthma and that the risk of asthma-related hospitalizations and emergency department visits are increased for patients with untreated rhinitis (6). In fact, allergic rhinitis and asthma share a respiratory mucosal eosinophilic inflammation and consequently require an integrated anti-inflammatory treatment to induce remission in symptoms. In this regard, thermal water has been commonly used for rhinitis since the Roman age. In particular, Ischia spas are very popular as more than 100,000 people attend them yearly. However, there is no scientific evidence of their activity on the respiratory tract.

The purpose of this study is to therefore evaluate the effects of Ischia thermal water nasal irrigation on nasal symptoms and airway inflammation in children with allergic rhinitis and intermittent asthma during the period of natural exposure to *Parietaria* pollen.

MATERIALS AND METHODS

Population

Forty children were selected from both the Department of Pediatrics, Second University of Naples and the Children's Hospital "Anna Rizzoli" of Ischia, Naples. All the selected children, aged 6-14 years, had to have: i) a history of seasonal moderate to severe allergic rhinitis for at least 2 years; ii) a sensitization to Parietaria (documented by positive skin prick test); and iii) a history of mild intermittent asthma (documented by symptoms and positive bronchodilation test). The sample size was determined considering a presumed reduction of nasal symptoms of 20% in Group 1. Patients who had used long-acting bronchodilators, antihistamines, intranasal, bronchial or systemic corticosteroids, cromolyn sodium, and leukotriene modifiers in the previous 6 weeks were excluded from the study. Other exclusion criteria were the presence of a sinus and/or upper or lower respiratory tract infection, persistent asthma, nasal surgery within the last year, respiratory tract abnormalities or systemic diseases. All selected children and their parents were informed about the rationale and the way in which the study had to be conducted and had signed an informed consent. The study was approved by the local Ethics Committees. The study was registered in the Clinical Trials.gov (NCT01326247).

Thermal water

The study was conducted on the island of Ischia (a volcanic island) in the Bay of Naples, the thermal waters of which have been used since ancient times for the treatment of many respiratory tract diseases. On this island there are several different thermal water pools. In this study the water of "Lacco Ameno", that can be defined as "hyper-mineral chloride sodium water", was used; its characteristics are reported in Table I.

Study design

The study was conducted on the island of Ischia, Naples from April to June 2009, during the natural exposure period to Parietaria pollen (Fig. 1). The treatment started just before the pollen season, when all the children were asymptomatic, not treated with any drug, and not affected by respiratory tract and systemic diseases. All children were randomly divided into two homogeneous and parallel groups by gender and age with a ratio 1:1 using a predetermined casual random allocation defined by MMdG (Table II). The first group (group 1) practiced crenotherapy with "hyper-mineral chloride sodium water" aerosol by nasal adapter for 15 days per month, for three consecutive months, at thermal spa services of Lacco Ameno, while the control group (group 2) was treated daily, in the same period, by a micronized nasal douche with 0.9% NaCl (isotonic) solution. In addition, all children were treated on demand with cetirizine (0.5 gtt./kg/day once daily); no other therapy was permitted. Before the treatment (T0), at the end of the treatment (T1) and again 2 weeks after the end of the treatment (T2), all the children performed spirometry (Pony FX Cosmed), and exhaled nitric oxide (FeNO) (NIOX MINO analyzer COSMED) measurement, to assess their airway inflammation (7-9). At the time of recruitment, the parents of the children were instructed to fill a specific diary-card at home, to assess rhinitis symptoms and possible drug use during the 3-month treatment period. The symptoms considered in the total symptom score (TSS) were: nasal obstruction, sneezing, nasal discharge and itching. These symptoms were scored: 0 = absent symptom, 1 = mild (symptom present but not annoying), 2 = moderate (frequent and offensive symptom but not interfering with sleep or normal activities) 3 = severe (symptom

interfering with sleep or normal activities). Every two weeks, at the end of each cycle of therapy the children underwent a general clinical control with nasal endoscopy, spirometry and monitoring the completion of diary cards and the possible use of drugs.

Statistical analysis and data definitions

The first outcome was the effect on nasal symptoms, the secondary outcome was the effect on airway inflammation. Descriptive statistics were taken and quantitative parameters were reported as means and standard deviations (SD). Qualitative data were reported as frequencies and percentages. Comparison of qualitative data among the two groups of patients was made by the *chi*-square test (or by the Fisher's Exact test in case of expected frequencies less than five).

The Mann-Whitney test was used as a nonparametric counterpart. The ANOVA Friedman test was used to compared clinical data (FEV_1 % of predicted, FeNO in ppb), in the two groups of patients at each visit.

For the analysis, a p value < 0.05 was considered significant. The mean ± SD and SE was used in the graphs. A statistical software program (StatSoft Italia s.r.l. 2005. Statistica, Vigonza, Italy) was used for all the analyses.

RESULTS

Of the 40 children enrolled, the outcome of 34 children, 14 males and 20 females, was examined, because 4 children (3 children in Group 2) left the study as they had used topical nasal corticosteroids and another one of Group 2 had assumed leukotriene modifiers. Moreover, one child in Group 1 was released from the study because he had not returned for the control. The results obtained in 18 children of Group 1 were compared to those of 16 children in Group 2. The two groups were found to be statistically homogeneous and comparable at baseline (Table II).

With regard to the rhinitis symptoms, the analysis of diary cards showed a significant reduction in Group 1 of the symptom score (mean ± SD 206.5±40.3) in comparison to Group 2, after three months of therapy (T1) (mean ± SD 316.2±66.2)

Table I. *Physical and chemical analysis of the water of "Lacco Ameno".*

Electrical conductivity specific	20°C 25°C	**15733** **17400**	µS\cm
Fixed residue at 180°C		**.....** **11114**	µS\cm
Silica	SiO_2	**158**	mg\l
Bicarbonate ions	HCO_3	**2042**	mg\l
Chloride ions	Cl	**4485**	mg\l
Sulphate ions	SO_4	**533**	mg\l
Sodium ions	Na	**3415**	mg\l
Potassium ions	K	**239**	mg\l
Calcium ions	Ca	**117**	mg\l
Magnesium ions	Mg	**127**	mg\l
Iron ions	Fe Fe	**2.5**	mg\l
Ammonium ions	NH_4	**< 0.02**	mg\l
Total phosphorus	P(V)	**< 1**	mg\l
Bisulfite ion (solfidrometric grade)	HS	< **0.5**	mg\l
Strontium ions	Sr	**0.1**	mg\l
Lithium Ion	Li	**0,1**	mg\l
Bromide ions	Br	**5**	mg\l
Barium ions	Ba	**0.6**	mg\l
Manganese ions	Mn	**1.2**	mg\l
Nitrate ions	NO_3	**26**	mg\l
Nitrite ion	NO_2	< **0.02**	mg\l
Total hardness		**……..** **81.3**	°Fr

Table II. *Baseline demographic and clinical characteristic of the 34 evaluated patients.*

	Group I N= 18	Group II N= 16	*P*-value
Gender- males, N (%)	8 (42.1)	6(40)	N.S.ǂ
Age (year) mean ± SD	9.7±1.7	9.4±1.9	N.S.*
FEV_1 mean ± SD, % of predicted	99.6±9.7	101.5±9.5	N.S.*
FeNO mean ± SD, in ppb	48.3±18.7	47.4±17	N.S.*

The *percentages in round brackets are calculated over the total number of subjects reported at the top of column.*
ǂ*: Chi-squared test.*
**: Mann-Whitney U test*

Table III. *Changes in FEV_1 and FeNO values between the two groups.*

	Group I			*P*-value	Group II			*P*-value
	T_0	T_1	T_2		T_0	T_1	T_2	
FEV_1 mean ± SD	99.6±9.7	96.6±10.4	97.5 ±9.3	N.S*	101.5±9.5	99.1±8.8	97.8 ±5.3	N.S.*
FeNO mean ± SD, in ppb	48.3±18.7	19.2±8.4	19.3±6.6	< 0.05*	47.4±17	53.4 ±21.6	46.8±21.1	N.S.*

**: Anova Friedman test*

(Mann-Whitney U test, p = 0.000023) as reported in Fig. 2A.

Regarding the eosinophilic airway inflammation monitored by exhaled nitric oxide (FeNO), at the time recruitment (T0) both groups had comparable levels of FeNO (Table II). Analyzing the values of FeNO in Group 1 there was a statistically significant reduction in the mean FeNO levels between T0 and T1 and between T0 and T2 ($p < 0.05$), but not between T1 and T2 (p = NS) (Table III). In Group 2 there were no significant differences between the FeNO values during the treatment and after the follow-up period (Table III). The comparison of the values of FeNO between the two groups at the end of treatment (T1) shows that Group 1 had significantly lower FeNO values than the children in group 2 (p = 0.0001) (Fig. 2B). A significant reduction of the FeNO values was still present only in Group 1 two weeks after the end of the therapy (T2) (Fig. 2B). There was a statistically significant correlation between rhinitis symptoms score and FeNO values ($p<0.0001$) at T1 (Fig.4). However, there were no statistically significant differences between the two groups in FEV_1 values before and after the treatment (Table III).

There were no significant side effects in either

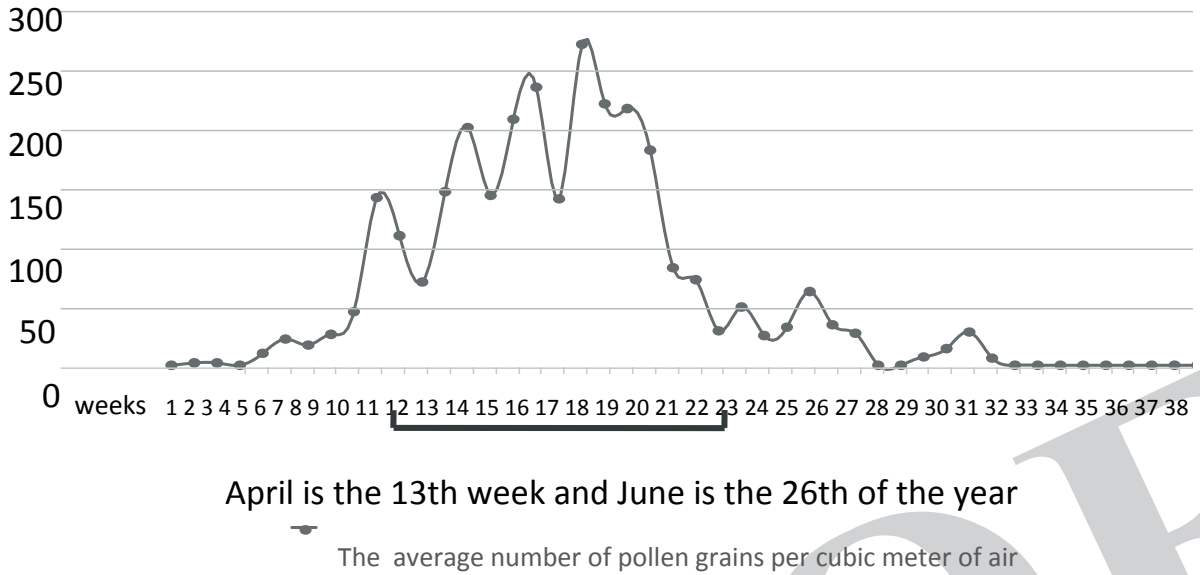

Fig. 1. *Parietaria pollen count in Ischia; data from http://www.pollinieallergia.net*

group. No important changes to methods and to outcomes occurred after the start of the trial.

DISCUSSION

Previous studies have shown that the waters of marine origin were able to interfere with allergic inflammation (5) and that nasal rinsing with hypertonic saline can improve symptoms of rhinitis and drug consumption in children with pollen allergic rhinitis (3). The present study demonstrates that intranasal crenotherapy with the hyper-mineral chloride sodium water of Ischia was effective in treating children with allergic rhinitis to pollens. It is to note that the considered pollen season was substantially comparable to previous ones.

Thermal water induced a significant reduction in rhinitis symptoms, assessed by the TSS, only in Group 1. Compared to the nasal irrigation with 0.9% chloride sodium solution, that can simply clean the nasal mucosa, it is likely that the crenotherapy with the hyper-mineral chloride sodium water of Ischia had an adjunctive effective anti-inflammatory effect on the nasal mucosa, because it can interfere with the allergic inflammation. The hyper-mineral chloride sodium waters of Lacco Ameno (Ischia) take their origin from rainwater and from sea water. They are hypertonic waters, made up by mainly of chloride sodium, sulphate, bicarbonate and magnesium and are known for their ability to activate muco-ciliary clearance and to carry out anti-oedema action. The anti-inflammatory activity of seawater on the respiratory mucosa has already been demonstrated in other studies (5, 10) and it is probably determined by the presence of natural minerals and trace elements in trace amounts (9). The hypertonicity of the thermal water of Lacco Ameno has probably contributed to its effectiveness; hypertonic saline solutions have already been tested in allergic rhinitis, and proved to be more effective than isotonic saline (3). In our study, anti-inflammatory activity of hyper-mineral chloride sodium water of Ischia is highlighted by the reduction in FeNO values in the treated group. There is a direct relationship between the anatomical

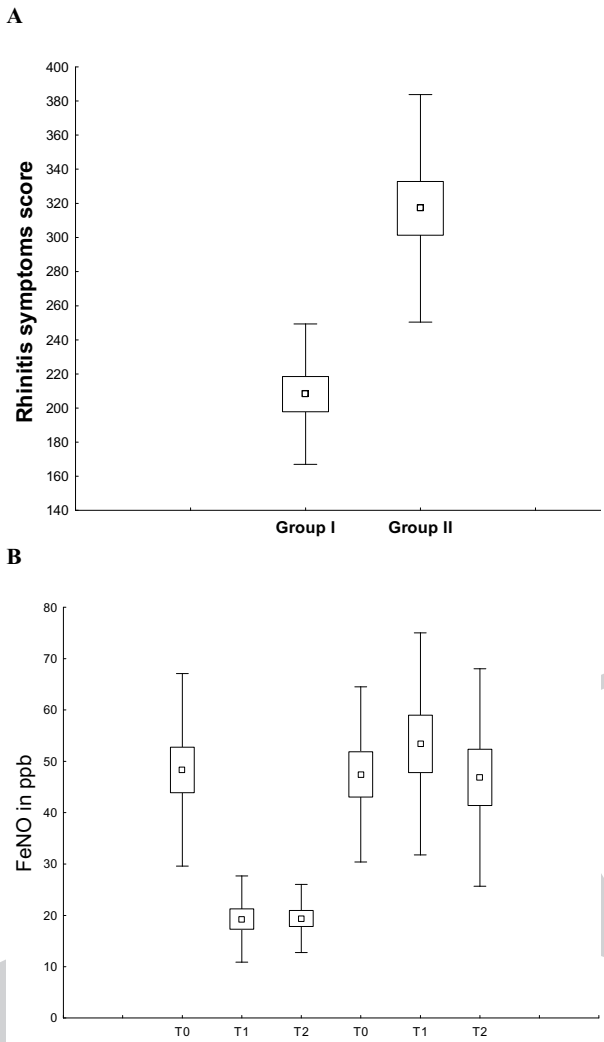

Fig. 2. ***A)*** *Rhinitis symptoms score in the two groups after the treatment (T2). Mann-Whitney U test, p = 0.000023.* ***B)*** *FeNO levels in the two groups at T0, T1, and T2. Mann-Whitney U test, p=0.0001*

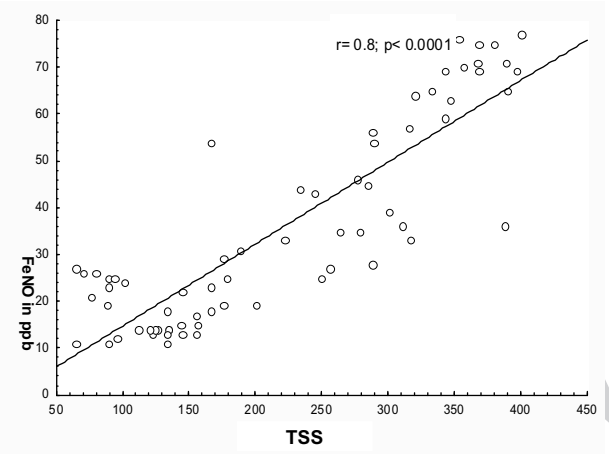

Fig. 3. *Relationship between TSS and FeNO values in group 1 at T1.*

and functional nasal and bronchial mucosa. It has been shown that allergic nasal inflammation can lead to eosinophilic airway inflammation through the release of chemotactic factors that stimulate the progenitors of eosinophils and basophils (11). Progenitor cells and the receptor for IL-5 are able to reach both the low and the upper airways. Therefore, nasal crenotherapy with hyper-mineral chloride sodium water of Ischia seems to have effectiveness on bronchial immune responses and inflammation. Both treatments have been proved safe and there were no significant side effects. Indeed, the large size of these inhaled particles does not allow their passage into the lower airways. As a consequence there were no significant changes in FEV_1 values in either groups.

However, this study has some limitations: a reduced number of participants, it is restricted to a selected population, and nasal function has not been assessed. Nevertheless, the findings could be applied to the model of allergic rhinitis treatment as the results may be considered clinically relevant.

In conclusion, this study shows that nasal crenotherapy with hyper-mineral chloride-sodium water of Ischia was effective in children with seasonal allergic rhinitis to Parietaria. These results demonstrate that this natural treatment was effective in a common and debilitating disease such as allergic rhinitis. Further studies are certainly needed to confirm the benefits of the waters of the thermal baths of Ischia in treating allergic rhinitis.

ACKNOWLEDGEMENTS

This study was supported by “Fondazione per la Ricerca Scientifica Termale” and “Centro Studi Julio Jasolino” grants.

REFERENCES

1. Meltzer EO, Blaiss MS, Derebery MJ, Mahr TA, Gordon BR, Sheth KK, Simmons AL, Wingertzahn MA, Boyle JM. Burden of allergic rhinitis: Results from the Pediatric Allergies in America survey. J Allergy Clin Immunol 2009; 124:S43-70.
2. Ciprandi G, Cirillo I, Pistorio A. Relationship between rhinitis duration and worsening of nasal function. Otolaryngol Head Neck Surg 2008; 138:725-29.
3. Garavello W, Romagnoli M, Sordo L, Gaini RM, Di Berardino C, Angrisano A. Hypersaline nasal irrigation in children with symptomatic seasonal allergic rhinitis: a randomized study. Pediatr Allergy Immunol 2003; 14:140-43.
4. Subiza JL, Subiza J, Barjau MC, Rodríguez R, Gavilán MJ. Inibition of the seasonal IgE increase to dactylis glomerata by daily sodium chloride nasal-sinus irrigation during the grass pollen season J Allergy clin Immunol 1999; 104:711-12.
5. Tabary O, Muselet C, Yvin JC, Halley-Vanhove B, Puchelle E, Jacquot J. Physiomer reduces the chemokine interleukin-8 production by activated human respiratory epithelial cells. Eur Respir J 2001; 18:661-66.
6. Crystal-Peters J, Neslusan C, Crown WH, Torres A. Treating allergic rhinitis in patients with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visits. J Allergy Clin Immunol 2002; 109:57-62.
7. Kharitonov SA, Yates D, Robbins RA, Logan-Sinclair R, Shinebourne EA, Barnes PJ. Increased nitric oxide in exhaled air of asthmatic patients. Lancet 1994; 343:133-35.
8. Cardinale F. Exhaled nitric oxide, total serum IgE and allergic sensitization in childhood asthma and allergic rhinitis. Pediatr Allergy Immunol 2005; 16: 236-42.
9. Howarth PH, Objective monitoring of nasal airway inflammation in rhinitis. J Allergy Clin Immunol 2005; 115:S414-41.
10. Traissac L, Bordenave L, Bareille R, Bacquey C, Courtes C. *In vitro* study of the effect of sea water by products on the respiratory mucosa. Rev Soc Fr ORL 1995; 32:43-49.
11. Braunsthal GJ, Kleinjan A, Overbeek SE, Prins JB, Hoogsteden HC, Fokkens WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. Am J Resp Crit Care Med 2000; 161:469-76.