ORIGINAL CONTRIBUTION

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Sulphurous thermal water inhalations in the treatment of chronic rhinosinusitis*

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SUMMARY

Introduction: *The aim of this study was to evaluate the efficiency of sulphurous thermal water in the treatment of chronic rhinosinusitis (CRS).*

Methods: *Eighty patients with CRS were included and randomly assigned into two groups. Patients underwent a 12-day course of warm vapour inhalations and nasal irrigations with sulphurous thermal water in group A, and a physiological solution in group B.*

Results: *Compared with group B, in group A the results were as follows: serum concentration of IgE was significantly lower ($p < 0.05$) 12 days (76.27 ± 26.3 mg/dl vs. 97.44 ± 45.4) and 3 months after the beginning of the treatment (75.48 ± 26.1 mg/dl vs. 98.37 ± 41.4); IgA titers were not significantly higher 12 days (231.09 ± 120.3 mg/dl vs. 220.44 ± 114.4 mg/dl) and 3 months after the beginning of the treatment (235.44 ± 118.5 mg/dl vs. 214.51 ± 111.8 mg/dl); VAS scores were significantly ($p < 0.05$) improved at 12 days (1.7 ± 0.18 vs. 6.9 ± 0.51) and 3 months after the start (1.8 ± 0.22 vs. 7.1 ± 0.59); NMTT was normal at 12 days (11.54 ± 1.59 min vs. 17.38 ± 1.83 min) and 3 months after the beginning of the treatment (11.46 ± 2.07 min vs. 17.43 ± 2.01 min); total nasal resistances were significantly ($p < 0.05$) decreased at 12 days and 3 months.*

Conclusion: *Our results indicate the efficiency and applicability of sulphurous thermal water in the treatment of CRS.*

Key words: chronic rhinosinusitis, inhalation, recurrent upper respiratory tract infectious, SPA mineral water, sulphurous water

INTRODUCTION

Chronic rhinosinusitis (CRS) is a group of clinical disorders that encompasses heterogeneous infectious and inflammatory conditions affecting the nose and paranasal sinuses. Estimates of the prevalence of CRS vary due to differences in the definition of rhinosinusitis and methods of diagnosis [(1)]. Until the first European Position Paper on Rhinosinusitis and Nasal Polyps was published, data on (chronic) rhinosinusitis were limited and the disease entity was badly evaluated [(2)]. Although it is often hypothesized that CRS evolves from acute rhinosinusitis, this has never been proven. Furthermore, the role of bacteria in CRS is far from clear and the clinical diagnosis is always been somewhat difficult, due to the difficulty to define the disease and the variety of presenting signs and symptoms. Corroboration of the definitive diagnosis of CRS should be done with nasal endoscopy [(2-4)].

A proper treatment should provide patients with adequate coverage of aerobic as well as anaerobic pathogens so as to minimize recurrences, enhance eradication, maximize compliance and avoid resistance. At present, patients affected by CRS are cured by means of corticosteroid and antibacterial therapy [(3,4)].

Because of antibiotic resistance increase, attention has been focused on the possibility of alternative approaches [(2,5,6)]. A number of randomized controlled trials have tested nasal irrigations in the treatment of CRS: because of their effects in terms of alleviation of symptoms, endoscopic findings and the like, nasal irrigations have obtained in the past years even more consensus when administered in patients affected by CRS [(2,7)].

Nasal irrigation is widely used in treating sinonasal diseases: not only does it remove static secretions and promote mucociliary clearance, but, in chronic rhinosinusitis, nasal flush is also a potential route for topical drug administration into paranasal sinuses. For these reasons, nasal irrigation may be a valid alternative treatment [(8)].

The aim of this study was to evaluate the efficiency of sulphurous thermal water and to approach the mechanism of their effect in the treatment of CRS.

METHODS

This double-blinded study was conducted according to the *Revised Declaration of Helsinki* and *The Good Clinical Practice Guidelines*. All procedures were carried out in accordance with the local ethics committee's protocol.

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Patient population

A total of 80 patients (45 males and 35 females) aged between 26 and 58 years (46.4 years old on average) with CRS were included, between September 2008 and December 2008. The diagnosis of CRS was made following EPOS guidelines of which an update was published in Rhinology in 2007 [2]. CRS was defined as presence of two or more symptoms, for at least 12 weeks, one of which is either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip): ± facial pain/pressure, ± reduction or loss of smell [2]. The differentiation between CRS and nasal polyps (NP) was based on out-patient endoscopy: at baseline, nasal endoscopy showed no visible polyps in the middle meatus and nasal cavity in all patients [2].

Exclusion criteria were: patients treated with immunostimulant or immunosoppressive agents in the previous 6 months; genetic and congenital condition (cystic fibrosis, primary ciliary dyskinesia); nasal polyps; positive allergy testing; anatomic abnormalities (severe septal deviation among others); acquired mucociliary dysfunction; neoplasms; acute contemporary bacterial and/or viral rhinosinusitis, middle ear and upper respiratory tract; bronchopulmonary disease; nasal trauma; smoker; previous nasal and sinus surgery.

Study design

After signing an informed consent, at baseline, 12 days and 3 months after the beginning of the treatment, all patients underwent medical history, ENT examination by an ENT specialist with nasal endoscopy, nasal swabbing, plasma levels of immunoglobulins class E, G, A, M (IgE, IgG, IgA, IgM), nasal mucociliar transport time (NMTT) determination, subjective assessment of symptoms by visual analog scale: a standard 10 cm visual analog scale (VAS) ranging from 0 (no symptoms, satisfied with the situation) to 10 (the most severe symptoms, dissatisfying situation) was used to assess the subjective symptoms and anterior active rhinomanometry.

Nasal mucociliar transport time determination

NMTT was evaluated by the saccharin test at the beginning, at the end and three months after the start: saccharin transit time was measured after depositing 15 mg of 2% sodium saccharin behind the anterior margin of the inferior turbinate. The patient was instructed to sit with his head inclined forward at an angle of 10°; during the test, the patients had to swallow every 30 seconds and had to avoid blowing their nose. The test was stopped when the saccharin was tasted.

Rhinomanometry

Anterior active rhinomanometry (Rhinomanometer SR 2000, Medtronic, Italy) was performed according to the International Committee for the Standardization of Rhinomanometry (ICSR) guidelines; the flow was evaluated at a transnasal pressure of 150 Pa [9]. Frequency, severity and social impact of CRS episodes were also adopted as valid criteria; at each control the following parameters were checked: number of acute episodes (acute rhinosinusitis >1), presence of fever (yes/no), use of ancillary therapy (none / symptomatic only / antibacterials and/or corticosteroids), medical consultation (yes/no).

Table 1. Statistical analysis of the baseline characteristics between the two groups. p= p value; N: number of patiens; A: mean age; M: male; F: female.

	Group A	Group B	p
N	40	40	$p > 0.05$
Age	46.1	46.7	$p > 0.05$
Sex	23M/17F	22M/18F	$p > 0.05$
IgE	106.26 ± 31.4	102.18 ± 36.9	$p > 0.05$
IgG	1158.33 ± 201.9	1151.44 ± 204.9	$p > 0.05$
IgM	152.22 ± 53.7	154.46 ± 55.9	$p > 0.05$
IgA	213.66 ± 111.2	215.37 ± 110.2	$p > 0.05$
VAS	7.8 ± 0.39	8.2 ± 0.44	$p > 0.05$
NMTT	19.01 ± 2.11	18.34 ± 2.04	$p > 0.05$

Nasal irrigation

The patients were randomly assigned into two numerically equal groups (A and B). Random allocation sequence was done through numbered containers. At baseline, the characteristics of both groups are described in Table 1. All patients underwent a 12-day course warm inhalation (38°C, at a distance of 20 cm from the patient's face for 10 min), with nasal irrigations. Nasal irrigation, which followed the inhalation, was done through an electrical irrigation device, which pumped the solution through a flexible tube, in connection with a nasal adapter, with water regulated on corporeal temperature for six min.

Treatments were performed in the ENT Department of the University of Genoa, once a day for 12 consecutive days. Group A recieved sulphurous thermal water from The Tabiano SPA Mineral Water (Tabiano, Parma, Italy); the chemical

Table 2. Essential chemical composition of sulphurous water (Tabiano Terme, Parma, Italy). Analysis by the ARPA laboratory of Reggio Emila on April, 5 2006.

Item	Result	Unit of measurement
Water temperature	15.6	C
Fixed residue 180°C	4120	mg/l
Ionian concentrations		
hydrogen pH	6.6	–
Solid residue at 180°C	3660	mg/l
Sulphydrate (HS^-)	156	mg/l
Sulphates ($SO4^{--}$)	1980	mg/l
Bicarbonates ($HCO3^-$)	608	mg/l
Sulphide (H2S)	160	mg/l
Sodium (Na^+)	330	mg/l
Chloride (Cl^-)	257	mg/l
Calcium (Ca^{++})	590	mg/l
Magnesium (Mg^{++})	134.5	mg/l
Hydrogen sulphide not ionized	110	mg/l
Nitrates ($NO3^-$)	<1	mg/l

Table 3. Mean plasma levels (mg/dl) of immunoglobulins class E, G, A, M (IgE, IgG, IgA, IgM), ± Standard Deviation, at baseline (t = 0) 12 days (t = 1) and 3 months after the beginning of the treatment (t = 2) for both groups. p = statistical analysis between t = 0 and t = 1, t = 2; p* = statistical analysis between the two groups.

	Group	Patients	t = 0	t = 1	p	t = 2	p
IgE	A	40	106.26±31.4	76.27±26.3	p<0.05	75.48±26.1	p<0.05
	B	740	102.18±36.9	97.44±45.4	p>0.05	98.37±41.4	p>0.05
p*		p*>0.05	p*<0.05		p*<0.05		
IgG	A	40	1158.33±201.9	1204.59±210.3	p>0.05	1199.5±197.4	p>0.05
	B	740	1151.44±204.9	1188.46±207.5	p>0.05	1193.97±206.4	p>0.05
p*		p*>0.05	p*>0.05		p*>0.05		
IgM	A	40	152.22±53.7	150.48±52.1	p>0.05	153.48±519	p>0.05
	B	40	154.46±55.9	155.48±54.3	p>0.05	153.63±52.8	p>0.05
p*		p*>0.05	p*>0.05		p*>0.05		
IgA	A	40	213.66±111.2	231.09±120.3	p>0.05	235.44±118.5	p>0.05
	B	40	215.37±110.2	220.44±114.4	p>0.05	214.51±111.8	p>0.05

analysis of thermal water is given in Table 2. Group B received a physiological solution (sodium chloride at 0.9%). To maintain double blind conditions, the colour (white) and taste (sulphur) of the solution used for vapor inhalation were similar in both groups. The medical doctors that administered the inhalation and the nasal irrigation and the medical doctor that assessed the outcomes were blinded to the group assignment.

After the 12-day course warm inhalation, with nasal irrigations, patients were free to use the ancillary therapy, when necessary. The following medications were allowed during the study: symptomatic (nasal decongestant, oral antistamines), oral antibacterials (200 mg cefpodoxine twice daily for 6 days) and oral corticosteroids (8 mg methylprednisolone three times daily for 5 days).

Statistical analysis

All the data were evaluated by the paired or unpaired t-test, and χ^2 analysis where appropriate; probability (p) values of less than 0.05 were regarded as significant. The results were reviewed and approved by the Institutional Review Board of the University of Genoa, Italy. Results for each group are expressed as means ± Standard Deviation (SD).

RESULTS

Immunoglobulins

In group A, we observed at 12 days (76.27 ± 26.3 mg/dl vs. 106.26 ± 31.4) and 3 months after the beginning of the treatment (75.48 ± 26.1 mg/dl vs. 106.26 ± 31.4) a significant ($p < 0.05$) reduction of serum concentration of IgE. Serum concentration of IgE was significantly lower ($p < 0.05$) in group A compared to group B when measured at 12 days (76.27 ± 26.3 mg/dl vs. 97.44 ± 45.4) and 3 months after the beginning of the treatment (75.48 ± 26.1 mg/dl vs. 98.37 ± 41.4). In both groups, there were no significant changes in the serum concentration of IgG, IgA and IgM before and after the treatment (Table 3).

VAS

Concerning the VAS scores, group A presented a significant ($p < 0.05$) improvement of the scores at 12 days (1.7 ± 0.18 vs. 7.8 ± 0.39); this improvement was confirmed three months after the beginning of the treatment (1.8 ± 0.22 vs. 7.8 ± 0.39), whereas, there were no significant differences between each visit in group B (Table 4).

Compared with group B, in group A the improvement was statistically significant ($p < 0.05$) at 12 days (1.7 ± 0.18 vs. 6.9 ± 0.51) and three months after the beginning of the treatment (1.8 ± 0.22 vs. 7.1 ± 0.59) (Table 4).

NMTT

Normal NMTT was present at 12 days (11.54 ± 1.59 min) and three months after the beginning of the treatment (11.46 ± 2.07 min) in group A; when the NMTT of group B was measured no significant change was noted at 12 days (17.38 ± 1,83 min vs. 18.34 ± 2.04) and three months after the beginning of the therapy (17.43 ± 2.01 min vs. 18.34 ± 2.04 min) (Table 4).

Compared with group B, in group A the improvement was statistically significant ($p < 0.05$) at 12 days (11.54 ± 1.59 min vs. 17.38 ± 1.83 min) and three months after the beginning of the therapy (11.46 ± 2.07 min vs. 17.43 ± 2.01 min) (Table 4).

Table 4. Mean VAS score and NMTT, ± Standard Deviation, at baseline (t=0) 12days (t=1) and 3 months after the beginning of the treatment (t=2) for both groups. p= statistical analysis between t=0 and t=1, t=2; p*= statistical analysis between the two groups.

	Group	Patients	t = 0	t = 1	p	t = 2	p
VAS	A	40	7.8±0.39	1.7±0.18	p<0.05	1.8±0.22	p<0.05
score	B	40	8.2±0.44	6.9±0.51	p>0.05	7.1±0.59	p>0.05
p*		p*>0.05	p*<0.05		p*<0.05		
NMTT	A	40	19.01±2.11	11.54±1.59	p<0.05	11.46±2.07	
(min)	B	40	18.34±2.04	17.38±1.83	p>0.05	17.43±2.01	
p*		p*>0.05	p*<0.05		p*<0.05		

Anterior active rhinomanometry

In group A, both left and right rhinomanometric measures showed a significant nasal flow decrease ($p < 0.05$) at 12 days (0.27 ± 0.05 Pa/cm^3 vs. 1.25 ± 0.54 Pa/cm^3) and three months after the beginning of the therapy (0.24 ± 0.04 Pa/cm^3 vs. 1.25 ± 0.54 Pa/cm^3). In group B, there were no significant differences between each visit (Table 5).

Compared with group B, in group A the improvement was statistically significant ($p < 0.05$) at 12 days (0.27 ± 0.05 Pa/cm^3 vs. 1.28 ± 0.39 Pa/cm^3) and three months after the beginning (0.24 ± 0.04 Pa/cm^3 vs. 1.12 ± 0.47 Pa/cm^3).

Clinical parameters

Compared with group B, group A experienced a significant improvement of all clinical parameters. In group A, the number of new acute episodes was significantly ($p < 0.05$) lower, compared to group B, at 12 days (2/40 vs. 12/40) and three months after the beginning of the therapy (6/40 vs. 21/40) (Table 6).

No patient in group A experienced fever during the study. In group B, 6/40 and 11/40 patients presented fever at 12 days and three months after the beginning of the therapy, respectively, (Table 6).

In group A, no patient required ancillary therapy at 12 days and 3 months after the beginning of the therapy while in group B, at the last visit, symptomatic medication was used in 24 patients, corticosteroids in 9 patients and antibiotics in 7 patients (Table 6).

In group A, at 12 days only 3 patients required medical consultation (group B: 21); no patients required medical consultation 3 months after the beginning of the treatment (group B: 7) (Table 6).

No patient experienced side effects. All patients tolerated sulphurous water inhalations easily and the discomfort for the odour was minimal. No patient was lost to follow-up.

Table 5. For both nasal cavities: total nasal resistance mean values (T), ± Standard Deviation, at baseline (t=0) 12days (t=1) and 3 months after the beginning of the treatment (t=2) in each group. p= statistical analysis between t=0 and t=1, t=2; p*= statistical analysis between the two groups.

		Anterior active rhinomanometry (Pascal/ cm^3)				
		t = 0	t = 1	p	t = 2	p
A	T	1.25 ± 0.54	0.27 ± 0.05	p<0.05	0.24 ± 0.04	p<0.05
B	T	1.31 ± 0.69	1.28 ± 0.39	p>0.05	1.12 ± 0.47	p>0.05
	p*	p*>0.05	p*<0.05		p*<0.05	

Table 6. Number of patients with acute episodes (> 1), fever, use of ancillary therapy, medical consultation at 12days (t = 1) and 3 months after the beginning of the treatment (t = 2) for both groups. N: none; S: symptomatic; A: antibacterials; C: corticosteroids. p = statistical analysis between t = 0 and t = 1, t = 2; p* = statistical analysis between the two groups.

		Group	t = 1	t = 2	p
Acute episode		A	2/40	6/40	p>0.05
		B	12/40	21/40	p<0.05
			p*<0.05	p*<0.05	
Fever (yes/no)		A	0/40	0/40	p>0.05
		B	6/40	11/40	p<0.05
p*			p*<0.05	p*<0.05	
Ancillary therapy	N		24/40	0/40	
required	S	A	16/40	0/40	p<0.05
	A			0/40	
	C			0/40	
	N		0/40	0/40	
	S	B	18/40	24/40	p>0.05
	A		15/40	7/40	
	C		7/40	9/40	
p*			p*<0.05	p*<0.05	
Medical		A	yes (3/40)	yes(0/40)	p>0.05
consultation		B	yes (21/40)	yes (7/40)	p<0.05
(yes/no)					
p*			p*<0.05	p*<0.05	

DISCUSSION

CRS constitute a serious problem worldwide. CRS has multiple causes that include infectious (viral, bacterial, and fungal), allergic, genetic or congenital mucociliary dysfunction, immunodeficiency and systemic disorders. Although the presence of bacteria in CRS has been well documented, whether bacteria play a direct or indirect role in the development of CRS has not adequately determined [10].

Some patients experience considerable morbidity as a result of CRS and receive repeated courses of antibacterials that are not effective against viral infections and can increase bacterial resistance. Several causes of CRS are associated with viral upper respiratory tract infections (URTI): after the initial nasal exposure, the virus is attached to intracellular adhesion molecule 1, resulting in the activation of several inflammatory pathways [11].

Because acute rhinosinusitis is almost always infectious, it is marked by a normal T helper (Th)1-type of inflammation that is associated with a recruitment of neutrophils as the predominant cell type to fight infection. In contrast, most CRS has an atopic Th2 – type inflammatory response where eosinophils are the predominant inflammatory cells in both atopic and nonatopic individual with CRS. For these reasons, sulphurous thermal waters inhibit the inflammatory process [2,8].

Defects in the immune systems are well known to be linked with frequent respiratory tract infections. Defects in the immune system, such as common variable immunodeficiency and the more frequent selective IgA deficiency, are known to be linked with URTI caused by bacteria and viruses [2,8].

Modulation of the immune system by sulphurous water has been highlighted by different reports [8,12]: in vitro studies have shown that sulphurous thermal water can inhibit the prolifera-

tion of normal lymphocytes and T cells obtained from patients with chronic immunomediated diseases. Also, it was reported that sulphurous thermal waters can inhibit interleukin 2 (IL-2) and interferon (INF)-γ release from Th1 lymphocytes, suggesting that sulphurous water inhalation can modulate some physiopathological aspects of the memory T lymphocyte cells. It is known that INF-γ and IL-2 are the cytokine firstly activate with the consequent induction of other proinflammatory mediators [8,12].

The increased level of IgA highlights the anti-inflammatory effect of this thermal water [13]. After sulphurous water inhalation, the higher serum concentration of IgA can be attributed to an increased production of this immunoglobulin, since sulphur supports the assembly of the polypeptide chain.

These findings indicate that the sulphurous water have an immunomodulant activity that contributes to the therapeutic effects of the water in upper airway inflammatory diseases.

Data in the literature have demonstrated the therapeutic effects of mineral waters depend on their physical and chemical properties. The Tabiano water is cold-source, highly mineralised (sulphate-, calcium-, magnesium type) with a high bicarbonate (about 600 mg/l) and a very high hydrogen sulphide content. It is a sulphurous-sulphate-calcium-magnesium water with one of the highest levels of sulphur in the world. The natural balance between gases (hydrogen sulphide) and substances (sulphates, bicarbonates, calcium and magnesium) explains its general and local properties [12-17] (Table 2).

This water has antibacterial effects: only few microorganisms can survive in a sulphurous water because of the toxicity of sulphide [14]; sulphates, beside their bactericidal activity, also possess some anti-pathogenic features by blocking the microbial adhesins' synthesis [18].

Recent investigations have found that several bacteria form biofilms in the sinuses that may lead to recalcitrant sinus diseases [19]. Bacteria biofilms are a complex organization of bacteria anchored to a surface [19]. The pathogenicity of biofilms is magnified by two biofilm characteristics: the increased resistance or tolerance to antimicrobials and the inability of the host's defence mechanisms (phagocytes, antibodies) to be efficient against the bacterial cell domponent of the biofilm community [19]. By blocking the microbial adhesins' synthesis, this sulphurous thermal water may stop the biofilm production [18].

Mucociliary function represents the first barrier of the upper respiratory tract mucosa against various biological and physical insults. Our results confirm that sulphurous thermal water allows the improvement of mucociliary function, as confirmed by a significant reduction of mean mucociliary transport time: this function commonly prevents organic, inorganic, bacterial or viral particles from entering the organism [15].

Recent findings indicate trophic effects on respiratory mucosa and a mucolytic activity. The sulphurous water has antioxidant activity that contributes to the therapeutic effects of the water in upper airway inflammatory diseases: the inhalation of sulphurous thermal water can modulate its antioxidant activities of the sulfhydryl or thiolic group in the cysteine of glutathione or various low-weight soluble molecules [14,15]. In chronic inflammatory processes characterized by the presence of mucus in the upper respiratory tract, thermal therapy with sulphur mineral water induce beneficial effects on secretions. The sulphurous water acts on the mucoproteins to open disulphide bonds and consequently lower the viscosity of the mucus [14,15].

The improvement of the subjective symptoms (Table 6) shows the efficiency of an association between inhalation and nasal irrigation. The efficacy of inhalation depends on various factors influencing particles deposition in the airways, such as the type of adopted nebuliser, particles' size, airways calibre and patient's breathing pattern. The nebuliser is able to produce particles with a diameter of less than 3 μm that can reach the smaller bronchioli. The vapour penetration in the respiratory tissues determines a marked osmotic action that allows the water to improve nasal mucociliary clearance and reduces exposure to irritans: contact with an infectious agent might exert profound modifications on the immune system leading to the generation of inappropriate immunological response [13,20,21].

Eosinophils are present within the mucus and tissue of CRS patients and appear to be a marker of the disease. This hypereosinophilia correlates with a high level of serum concentration of IgE [22]. The decreased serum concentration of IgE confirms as the nasal irrigation and inhalation with sulphurous water can provide beneficial effects in chronic inflammatory disorders by inhibiting the immune response at a local level and cleaning the respiratory mucosa from the irritants [20].

In particular the irritants cause an autonomic nervous system reaction, characterized by parasympathetic nervous system predominance, resulting in engorgement of the turbinate vasculature and intercellular leakage of plasma and seromucinous discharge. These modifications justify the pre-treatment data observed in both groups with the anterior active rhinomanometry. The improvement observed in group A shows the decongestionant effect of the sulphurous thermal water on the turbinate.

With the emergence of resistant strains and the change in the distribution of bacterial flora over the time, preventive strategies may represent a valid alternative approach. For these reasons, thermal treatment could represent the first alternative choice to drugs in chronic, nonresponsive inflammatory diseases. The results of this study highlight that inhalation of sulphurous thermal water has a positive impact on the therapeutic strategy of CRS by a synergistic anti-bacterial/biofilm role and an anti IgE/eosinphillia role [23,24].

CONFLICT OF INTEREST

None of the authors have a financial relationship with any organization that sponsored the research. All the authors declare no financial, equipment or other support from third parties, companies or manufacturer.

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