

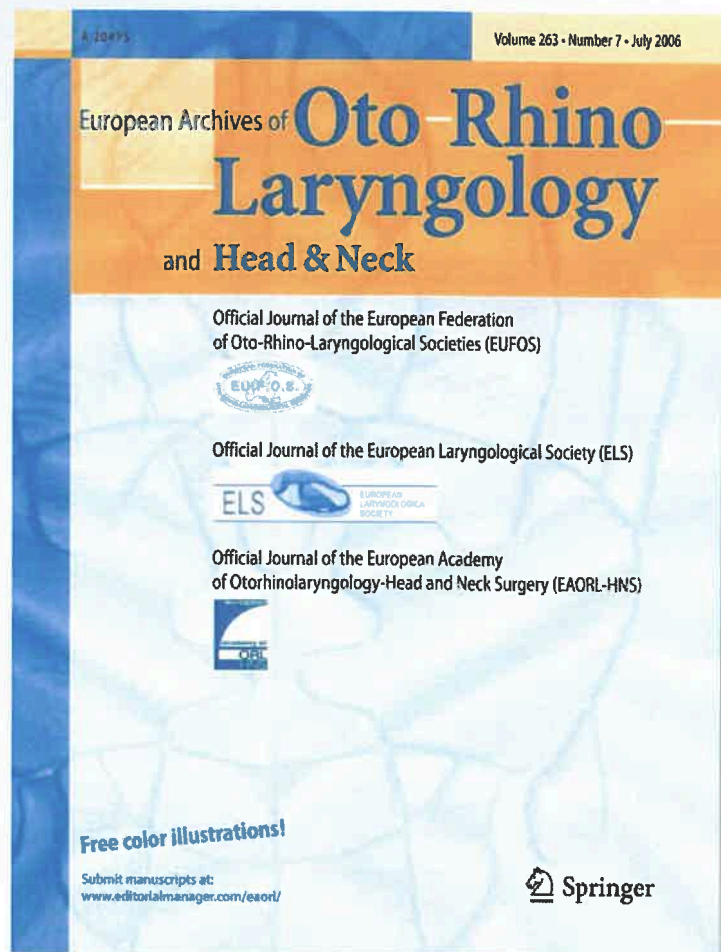
# *SPA therapy of upper respiratory tract inflammations*

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## SPA therapy of upper respiratory tract inflammations

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**Abstract** The upper airway respiratory diseases (i.e. common cold, allergic rhinitis, nonallergic/vasomotor rhinitis, acute and chronic rhinosinusitis and nasal polyposis) in which nasal congestion is a common symptom are often undertreated due to the frequent inadequate efficacy and safety concern with current therapies. In scientific literature, few studies seem to support the hypothesis that nasal inhalatory treatment with thermal water promotes the improvement of nasal symptoms, even if the mechanisms by which the improvement from SPA therapy can be expected remain debated. A prospective comparative study with a pre–post design has been performed consecutively enrolling 33 (males 70 %) patients of both genders older than 12 years of age, affected by chronic sinonasal inflammation. All patients underwent a 14-days course of radioactive water warm vapour inhalations followed by nasal aerosol of the same thermal water 10 min each once/day at Merano Terme. At the beginning and end of the study, in all the subjects, nasal function evaluation by active anterior rhinomanometry, mucociliary transport time (MCTt) determination and nasal cytology were performed. After the

inhalatory treatment, the mucociliary function was improved and the pathologic mucociliary transport times recorded at the beginning of the study being significantly reduced to physiologic ones. Besides, before treatment, the cytologic picture showed an inflammatory cell infiltration (eosinophils, neutrophils with/without bacteria, mast cells) in 37 % of patients; after therapy in 66 % of these patients, the rhinocytogram was normal. Our results suggest, according to the literature data, that SPA therapy with radioactive water could represent an alternative choice in chronic inflammatory diseases of the upper airways, nonresponsive to pharmacological therapy.

**Keywords** URTI · SPA therapy · Sinusnasal pathology

### Introduction

Nasal congestion, which may be described as a feeling of blockage or restricted airflow, often accompanied by aural fullness, is a common symptom in acute and chronic inflammatory processes of the nose and paranasal sinuses (i.e. common cold, allergic and nonallergic rhinitis, acute and chronic rhinosinusitis and nasal polyposis [1]).

Nasal obstruction, besides limiting the quantity of air intended for pulmonary respiration and thus reducing the oxygen supply to the entire organism, impairs the normal aeration of the nasal sinuses and middle ear causing CO<sub>2</sub> accumulation. This in turn, stimulates sinus pH reduction and the production of mucus that cannot be drained due to the oedema constricting the sinus and tube ostia, promoting stasis of secretions, and thus providing fertile ground for proliferation of germs [2].

The airway epithelium is a complex physico-chemical and functional barrier against pathogens, allergens and

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pollutants: it plays a central role to the defence of the respiratory tract, through the combined function of mechanical barrier, clearance through the mucociliary transport of ciliated and secretory cells and a variety of other innate and acquired immune defence mechanisms [3, 4].

When the epithelial barrier is damaged with cilia loss and excessive mucus formation, an inflammatory process is induced in an attempt to block antigens and allergens by releasing pro-inflammatory chemokines and cytokines [5].

The management of recurrent and chronic airway inflammation requires the integration of several different components: minimizing risk factors, educational programs, improving symptoms with a stepwise treatment approach and preventing recurrences. Although various pharmacotherapy options exist, no agent is universally efficacious, and there is a paucity of data supporting commonly used symptomatic therapies [1].

Inhalation of thermal water is traditionally used as part of the treatment of chronic sinonasal diseases and chronic bronchitis, but is not included among management options by the most recent guidelines, since uncertainty exists about indication; besides, the therapeutic mechanism of thermal water inhalation, its benefit and the underlying physiopathological mechanisms are not yet well clarified [6].

Mineral waters are classified according to their main physical and chemical characteristics (temperature, pressure, ionic concentration, radioactivity, and presence of specific ions or active chemical groups).

Besides the action of cleansing, massage, secretion dilution common to all, each thermal waters has typical therapeutical features and biological functions on the immune, cardiovascular and neuro-vegetative system [7].

The present study was conducted to evaluate the clinical effectiveness of warm vapour inhalation and nasal aerosol of radioactive (481 Bq/l Radon) hydrofluoric oligomineral water (Merano Terme) in patients with chronic nasal obstruction. Particularly, since objective methods are strongly recommended for use in the evaluation of pharmacologic agents that are expected to improve nasal airflow, endoscopic assessment was bilaterally performed and nasal obstruction was objectively assessed measuring nasal airflow resistance through active anterior rhinomanometry (AAR), and evaluating the mucociliary transport time (MCTt). Moreover, nasal cytology was also assessed.

## Methods

### Study design

A prospective comparative study with a pre-post design has been performed consecutively enrolling at the Merano

Therme in Merano (BZ) Italy, 33 patients of both genders (males 70 %) older than 12 years of age, affected by chronic sinonasal inflammation. The main inclusion criterion was nasal obstruction evaluated by a 10 points Visual Analogue Scale (1 = nasal airways completely free; 10 = nasal airway completely blocked) higher than 7 in the previous 2 months. Clinically speaking, patients affected by chronic rhinosinusitis, persistent allergic rhinitis, and vasomotor rhinitis with inferior turbinate hypertrophy were included.

The comparative study was the one by Marullo and Abramo [8]: in this research, 37 adults subjects affected by chronic catarrhal inflammation of the nose and paranasal sinuses were treated by warm inhalation and aerosol with same thermal water; a control group of 20 subjects, selected according the same clinical characteristics were treated by warm inhalation and aerosol with natural water. The results of AAR, MCTt and nasal cytology before and after treatment were analysed.

Patients affected by acute viral rhinitis or obstructive polyposis were excluded; patients with a history of nasal steroid and vasoconstrictive drug therapies or systemic NSAIDs (nonsteroidal anti-inflammatory drugs), oral steroids or mucolytic treatments in the previous 2 months were also excluded from the study.

At the study enrollment, patients older than 18 years and parents of patients younger than 18 were asked for their verbal and written informed consent.

All patients underwent a 14-days course of warm vapour inhalations (20 cm from patient's face), the device distributes thermal water at a temperature of 38 °C in 8–10 µm micelles laying down on the mucosa of upper airways. This treatment was followed by aerosol of the same thermal water (2–4 µm micelles reaching the lower airways), each treatment lasting 10 min/day.

The double administration of thermal water by inhalation and aerosol is aimed at curing both upper and lower airways: during the past decades in fact, our understanding of the coexistence of upper and lower airway diseases has evolved because of epidemiological studies [9], new physiopathological and immunological acquisitions on the respiratory tract [10], as well as studies on the effects of medical treatment of sinonasal district [11] and FESS on lower airway hyper reactivity [12].

The treatment was performed at the thermal station. The chemical analysis of the water is given in Table 1.

Anagraphic data, clinical history collection and ENT examination were performed before and after inhalatory treatment. Moreover, nasal airflow resistances were measured by active anterior rhinomanometry according to validated criteria [13, 14] and MCTt [15] was measured with an inert, coloured tracer (charcoal powder) mixed with 3 % saccharine. Finally, nasal cells harvested from the head of inferior and middle turbinates

**Table 1** Essential chemical composition of Merano Thermal water (Merano, BZ, Italy)

Parameters	Results	Unit of measurement
Atmospheric pressure	981	mbar
Air temperature	22	°C
Temperature at source	23.4	°C
Colour	Colourless	
Odour	Odourless	
Savour	Normal	
Deposit	Absent	
Acidity (pH)	7.48	u.pH
Conductivity (at source)	77	µS/cm
Total hardness	3.2	°F
Alkalinity (as CO <sub>3</sub> <sup>-</sup> )	0	mg/L
Alkalinity (as HCO <sub>3</sub> <sup>-</sup> )	34	mg/L
Oxidability	<0.5	mg/L
Ammonium ion (NH <sub>4</sub> <sup>+</sup> )	<0.02	mg/L
Nitrites (NO <sub>2</sub> <sup>-</sup> )	<0.002	mg/L
Fluoride (F <sup>-</sup> )	1.3	mg/L
Chloride (Cl <sup>-</sup> )	<1.0	mg/L
Nitrate (NO <sub>3</sub> <sup>-</sup> )	0.6	mg/L
Sulphate (SO <sub>4</sub> <sup>-</sup> )	9	mg/L
Radon concentration	246	Bq/L

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using a brushing technique were placed on a microscopic slide and fixed immediately for cytopathologic examination. A May–Grunwald’s–Giemsa stain was performed. All specimens were examined under light microscopy, evaluation was carried out at ×1,000 magnification and 10 representative microscopic fields for each slide were examined. The quantitative score of inflammatory cells was rated according to a scale previously described by Meltzer [16]. Bacterial and fungal presence in nasal mucosa was also evaluated.

#### Sample size calculation and statistical analysis

The study has been designed as a pre–post study comparing MCT times variation before and after treatment.

Sample size has been computed with reference to an alpha value of 0.05 and a power of 0.80, to detect an average difference of at least 3.5 s in MCTt after treatments as compared to mean MCTt levels before it, assuming a standard deviation of 3.5 MCTt, which was based on previously conducted pilot studies. Continuous variables were always expressed as median and interquartile difference and categorical variables as percentages and absolute numbers. Differences between nasal patency measurements before and after treatment were compared using Paired-Sample Wilcoxon Signed Rank

**Table 2** AAR and MCTt before–after measurements

	Before	After	<i>p</i>
<b>Nasal respiratory flow</b>			
Left ( <i>N</i> = 64)	252/332/460	250/388/506	0.532
Right ( <i>N</i> = 64)	267/346/499	222/408/522	0.586
Total ( <i>N</i> = 65)	512/672/912	580/740/1,014	0.55
<b>Nasal respiratory resistance</b>			
Left ( <i>N</i> = 64)	0.460/0.680/1.040	0.490/0.640/1.085	0.628
Right ( <i>N</i> = 63)	0.485/0.615/1.012	0.430/0.690/0.975	0.839
Total ( <i>N</i> = 53)	0.262/0.380/0.510	0.207/0.295/0.500	0.544
MCTt ( <i>N</i> = 65)	12/14/16	11/12/14	0.039

Numbers are I quartile/median/III quartile. *p* value refers to a significantly different distribution of each given variables before and after treatment with thermal water. Nasal respiratory flow is expressed in cc × s, nasal resistance in Pa/cc × s; mucociliary transport time (MCTt) in minutes

*N* number of valid cases for each variable

test and Chi-square test, as appropriate. Proportion of participants with adverse effects attributed to the treatment was also computed.

#### Results

All subjects completed the treatment and no adverse effects were reported.

The Wilcoxon test did not disclose a significant difference between pre- and post-treatment for nasal respiratory flow and nasal resistances (Table 2). Nasal resistance values were however within normal range at the end of treatment.

On the contrary, MCTt was significantly reduced after inhalatory treatment (Table 2) (*p* = 0.039).

Out of 33 patients, before the treatment, nasal cytology was normal in 18 subjects, while inflammatory cells infiltrate was present in 14 patients with or without bacterial presence (6 and 8 patients, respectively); in one case, the cytologic examination was impossible due to insufficient sample. In 66 % (9 patients) of those having pathological findings at first evaluation, nasal cytology was normal after the treatment (Table 3).

The comparative study [8] showed an improvement of all the considered parameters in the study group, but not in the control group.

#### Discussion

Even if the frequency of upper airways inflammation/infection has caused nasal congestion to become a highly prevalent

**Table 3** Nasal cytology, and bacterial and fungal presence before–after the inhalation therapy

	Before	After	<i>p</i>
<b>Epithelial cells (<i>N</i> = 64)</b>			
20–30	3 % (1)	3 % (1)	0.796
60–70	3 % (1)	0 % (0)	
70–80	25 % (8)	25 % (8)	
80–90	69 % (22)	72 % (23)	
<b>Goblet cells (<i>N</i> = 64)</b>			
05–10	12 % (4)	6 % (2)	0.16
10–20	12 % (4)	31 % (10)	
20–30	3 % (1)	0 % (0)	
30–40	72 % (23)	62 % (20)	
<b>Neutrophils (<i>N</i> = 62)</b>			
0	10 % (3)	16 % (5)	0.288
1+	61 % (19)	71 % (22)	
2+	0 % (0)	3 % (1)	
3+	26 % (8)	10 % (3)	
4+	3 % (1)	0 % (0)	
<b>Eosinophils (<i>N</i> = 62)</b>			
0	90 % (28)	94 % (29)	0.641
1+	10 % (3)	6 % (2)	
<b>Basophils (<i>N</i> = 62)</b>			
0	100 % (31)	100 % (31)	
<b>Mast cells (<i>N</i> = 62)</b>			
0	94 % (29)	97 % (30)	0.544
1+	6 % (2)	3 % (1)	
<b>Macrophages (<i>N</i> = 62)</b>			
0	100 % (31)	97 % (30)	0.313
1+	0 % (0)	3 % (1)	
<b>Lymphocytes (<i>N</i> = 62)</b>			
0	97 % (30)	97 % (30)	1
1+	3 % (1)	3 % (1)	
<b>Plasma cells (<i>N</i> = 62)</b>			
0	100 % (31)	100 % (31)	
<b>Bacteria (<i>N</i> = 64)</b>			
0	81 % (26)	91 % (29)	0.5
1+	3 % (1)	3 % (1)	
3+	16 % (5)	6 % (2)	
<b>Mycetes (<i>N</i> = 64)</b>			
0	100 % (32)	100 % (32)	

Absolute numbers of patients are reported in parenthesis. Number of patients with pathological inflammatory cells and bacteria before and after treatment are given in bold. *p* value refers to a significantly different distribution of each given variables before and after treatment with thermal water. The semiquantitative analysis and the inflammatory grading is made according to a scale previously described by Meltzer [16]

*N* number of valid cases for each variable

symptom, chronic rhinitis, rhinosinusitis are frequently undertreated due to the often inadequate efficacy or safety of current therapies [17, 18].

In the scientific literature, few studies seem to support the hypothesis that nasal inhalatory treatment with thermal water promotes the improvement of nasal symptoms even if the mechanisms by which the improvement can be expected remain debated.

The therapeutic effects of mineral waters depend on their physical and chemical properties; particularly, previous studies on the therapeutic effects of sulphurous waters on airway chronic inflammatory processes demonstrated beneficial effects on mucus secretions; the sulphurous water acts in fact on the mucoproteins to open disulphide bonds and consequently lower the viscosity of the mucus [19, 20]. Moreover, because of the toxicity of sulphide, this water has antibacterial effects [6, 19]. Finally, the sulphurous water also has an immunomodulant activity: after treatment with water, higher serum and secretion concentrations of IgA and decreased serum concentration of IgE have been observed in previous clinical studies [21]; moreover, nasal cytology evaluation has found a post-treatment reduction of neutrophil count [6].

In the present study, we evaluated different parameters of the respiratory mucosa including nasal perviousness, mucociliary clearance and nasal cytology; we examined 33 patients before and after inhalatory treatment with radioactive hydrofluoric oligomineral water of Merano Terme.

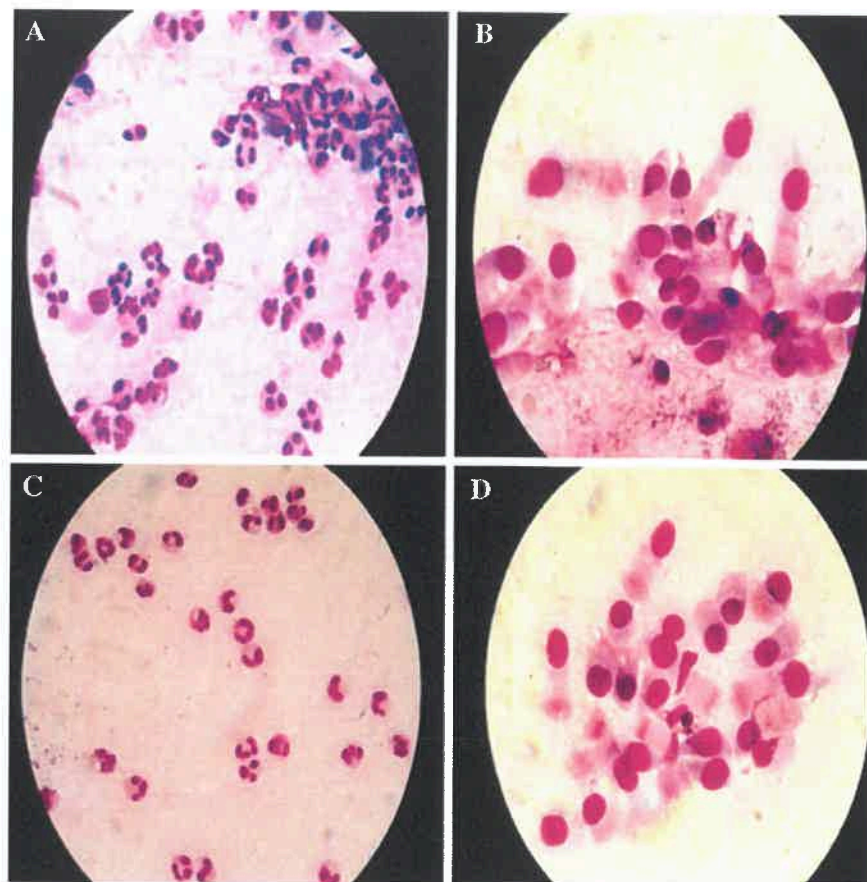
Whereas no significant changes were noted for nasal resistance values, we observed a significant improvement of the mucociliary function due to water inhalations. The pathologic median MCTt (reference values used were  $12.59 \pm 3$  min according to Passali and co-workers [22]) recorded at the beginning of the study being reduced to a physiological one after treatment.

Mucociliary transport is a physiological process that allows mucus to flow over an epithelial lamina of ciliated cells. It is an important defense mechanism against physical and biological insult in the nasal fossa, paranasal sinuses, and lower respiratory tracts. Inhaled foreign particles and microorganisms are caught by the mucus and transported towards the nasopharynx by means of nasal mucociliary activity. This process, which commonly prevents organic, inorganic, bacterial or viral particles from entering the organism, has a protective effect on the upper and lower respiratory system and is considered a first-line defense mechanism in humans.

The use of dye or radioactive tracers to measure MCTt has been available for nearly 30 years [22, 23]. It allows, if altered, one to recognize early alterations of rhinosinusal homeostasis. Although a crude measure, it has the advantage of considering the entire mucociliary system including cilia and periciliary mucous stratum.

More recent studies were performed with the aim of analysing the correlation between mucociliary clearance and rhinosinusal symptoms: Boatsman and co-workers [24] in a

**Fig. 1** Cytological picture in two patients before and after treatment by inhalation and aerosol with thermal water at Merano Thermal station. A neutrophilic infiltration is evident before the treatment (a, c), whereas a normal rhinocytogram can be observed after treatment (b, d). The prevalence of neutrophils is characteristics of all chronic inflammatory processes of the nose and paranasal sinuses



cross-sectional study on adult volunteers although stating that mucociliary clearance is important for the health of the sinusal cavities, could not find a clear correlation between rhinosinusitis symptoms severity as assessed by SNOT-20 scores and mucociliary transport times. On the contrary, Arnaoutakis and Collins [25], in children with symptoms of chronic rhinosinusitis, found a positive correlation between symptomatology and mucociliary transport times and velocity before and after adenoidectomy suggesting this test as a benchmark to demonstrate the specific symptomatic benefits from this surgical procedure.

In our previous experience, we demonstrated that in patients suffering from chronic sinonasal inflammation, the MCTt is delayed due to a reduction in the pericilia stratum and an increase in viscoelasticity of the mucus following the release of inflammation mediators [26].

The positive effect of the treatment with radioactive water was demonstrated also by the improvement of the rhinocytogram: in 66 % of the patients showing a pre-treatment inflammatory cells infiltration of the mucosa with abnormal number of neutrophils, eosinophils and mast cells with/without bacteria, the cytological picture was reduced to normal values after therapy.

Figure 1 reports the rhinocytogram before and after treatment in two different patients: the reduction of neutrophilic infiltration is evident.

As demonstrated in previous studies [8], the treatment with radioactive hydrofluoric oligominerals water has a positive effect in chronic aspecific inflammation of the upper respiratory tract: the impact on the mucociliary function and the cytological picture was evident, in some cases with a statistical significance in comparison with a control group treated with natural water: it could be supposed that besides the aspecific mechanical action of cleansing and drainage of secretions and inflammatory mediators, the radioactivity and the presence of fluorine ions characteristic of this water could have a denaturing and antiseptic effect on bacteria, viruses and allergens, thus decreasing the inflammatory load on the respiratory mucosa as confirmed also in the present study by the normalization of the cytological picture.

Due to the lack of side effects, thermal treatment could represent an alternative choice to pharmacological therapy in chronic, nonresponsive diseases of the upper respiratory airways.

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# Terapia termale nelle infiammazioni delle vie aeree superiori

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## **ABSTRACT**

**Premessa:** La congestione nasale è un sintomo comune delle patologie delle vie aeree superiori (raffreddore comune, rinite allergica, rinite non allergica/vasomotoria, rinosinusite acuta e cronica e poliposi nasale), spesso insufficientemente trattate a causa dei timori per la sicurezza e l'efficacia spesso inadeguata delle terapie attuali. Tuttavia, i risultati di alcuni studi pubblicati sembrano corroborare l'ipotesi che la crenoterapia inalatoria migliori i sintomi nasali, sebbene i meccanismi attraverso i quali ciò avviene siano ancora oggetto di dibattito.

**Metodi:** Questo studio prospettico "prima e dopo" è stato condotto arruolando consecutivamente 33 pazienti di entrambi i sessi (70% maschi), di età >12 anni e affetti da infiammazione sinonasale cronica. Tutti i pazienti sono stati sottoposti a un ciclo di 14 giorni di inalazioni di vapore di acqua radioattiva caldo, seguite da somministrazione di aerosol nasale della stessa acqua termale (micelle di 7 micron), ciascuna per 10 minuti al giorno presso le Terme Merano. All'inizio e al termine dello studio, la funzione nasale è stata valutata mediante rinomanometria anteriore attiva, determinazione del tempo di trasporto mucociliare e citologia nasale.

**Risultati:** La funzione mucociliare è migliorata dopo il trattamento inalatorio, come evidenziato dalla riduzione significativa dei tempi di trasporto mucociliari patologici registrati al basale. Inoltre, prima del trattamento, il 37% dei pazienti presentava un quadro citologico di infiltrazione di cellule infiammatorie (eosinofili, neutrofilii con/senza batteri, mastociti), mentre dopo la terapia il 66% di questi pazienti presentava rinocitogrammi nella norma.

**Conclusioni:** I nostri risultati indicano, in accordo con i dati di letteratura, come la terapia termale con acqua radioattiva possa offrire un'alternativa nel trattamento delle malattie infiammatorie croniche delle vie aeree superiori che non rispondono alla terapia farmacologica.

## INTRODUZIONE

La congestione nasale, che può essere descritta come una sensazione di blocco o restrizione del flusso d'aria, spesso accompagnata da pienezza auricolare, è un sintomo comune dell'infiammazione acuta e cronica del naso e dei seni paranasali, come quella causata da raffreddore comune, rinite allergica e non allergica, rinosinusite acuta e cronica e poliposi nasale [1]. Oltre a limitare la quantità d'aria per la respirazione polmonare, con conseguente riduzione dell'apporto di ossigeno all'organismo nel suo complesso, l'ostruzione nasale compromette la normale aerazione dei seni nasali e dell'orecchio medio e causa l'accumulo di CO<sub>2</sub>. Questo riduce il pH sinusale e provoca la produzione di muco che non riesce a defluire a causa dell'edema che comprime i seni e gli osti, favorendo la stasi delle secrezioni e creando un terreno fertile per la proliferazione dei germi [2].

La gestione integrata di questo processo patogeno prevede la riduzione dei fattori di rischio, programmi educativi, il miglioramento dei sintomi mediante un approccio di trattamento graduale e la prevenzione delle recidive. Sebbene vi siano diverse opzioni farmacoterapeutiche, nessuna è universalmente efficace e vi è una scarsità di dati a sostegno delle terapie sintomatiche più diffusamente utilizzate.

La crenoterapia inalatoria è tradizionalmente impiegata nell'ambito del trattamento delle patologie sinonasali croniche e della bronchite cronica, ma non è inserita tra le opzioni di trattamento raccomandate dalle più recenti linee guida, poiché la sua indicazione è incerta; inoltre, sono tuttora poco chiari il meccanismo terapeutico e il beneficio dell'inalazione di acqua termale, così come i meccanismi fisiopatologici di base [3]. Le acque minerali sono classificate in base alle principali caratteristiche fisiche e chimiche (temperatura, pressione, concentrazione di ioni, radioattività, presenza di ioni specifici o gruppi chimici attivi) e, oltre alla loro comune azione di depurazione, massaggio e diluizione delle secrezioni, ciascuna presenta caratteristiche terapeutiche tipiche e attività biologica specifica sul sistema immunitario, cardiovascolare e neurovegetativo. [4]

L'obiettivo di questo studio era valutare l'efficacia clinica delle inalazioni di vapore caldo e della somministrazione di aerosol nasale di acqua a base di oligominerali fluorurati radioattivi (481 Bq/l di

radon) (Terme Merano) nei pazienti con ostruzione nasale cronica. Poiché metodi obiettivi sono fortemente raccomandati nella valutazione di agenti farmacologici destinati a migliorare il flusso d'aria nasale, è stata eseguita un'endoscopia bilaterale e l'ostruzione nasale è stata valutata oggettivamente misurando la resistenza del flusso d'aria nasale mediante un rinomanometro anteriore attivo (AAR) e valutando il tempo di trasporto mucociliare (MCTt). È stata esaminata anche la citologia nasale.

## **METODI**

### *Disegno dello studio*

Questo studio prospettico "prima e dopo" ha arruolato consecutivamente 33 pazienti di entrambi i sessi (70% maschi), di età >12 anni e affetti da infiammazione sinonasale cronica che frequentavano le Terme Merano di Merano (Bolzano), Italia. I criteri di esclusione erano poliposi ostruttiva, anamnesi positiva per terapie farmacologiche con vasocostrittori e steroidi nasali, o farmaci antinfiammatori non steroidei (FANS) sistemici, trattamenti mucolitici o con steroidi orali nei due mesi precedenti.

Al momento dell'arruolamento nello studio, è stato ottenuto il consenso informato scritto dai pazienti di età  $\geq 18$  anni e dai genitori dei pazienti di età <18 anni.

Tutti i pazienti sono stati sottoposti a un ciclo di 14 giorni di inalazioni di vapore caldo (a 20 cm dal viso del paziente), seguite da somministrazione di aerosol nasale della stessa acqua termale (micelle di 7 micron), ciascuna per 10 minuti al giorno. La Tabella 1 mostra l'analisi chimica dell'acqua.

Dopo la raccolta dei dati anamnestici clinici e demografici, i pazienti sono stati sottoposti a una visita otorinolaringoiatrica (ORL). La resistenza del flusso d'aria nasale è stata registrata mediante AAR, secondo criteri validati [5,6], e l'MCTt (7) è stato misurato con un tracciante colorato inerte (polvere di carbone), miscelato con saccarina al 3%. Infine, le cellule nasali, prelevate mediante *brushing* della testa dei turbinati medi e inferiori, sono state collocate su un vetrino per microscopio e fissate immediatamente per l'esame citopatologico utilizzando colorazione di May Grunwald Giemsa. Sono stati esaminati dieci campi microscopici rappresentativi per ciascun vetrino, con microscopia ottica con ingrandimento x1000, ed è stato registrato il numero di cellule infiammatorie utilizzando una scala

descritta in precedenza da Meltzer [8]. È stata valutata anche la presenza di batteri e funghi nella mucosa nasale.

Gli esami sono stati ripetuti al termine del periodo di trattamento.

#### *Calcolo delle dimensioni del campione e analisi statistica*

Lo studio era stato concepito per confrontare la differenza tra l'MCTt prima e dopo il trattamento. Le dimensioni del campione sono state calcolate sulla base di un valore alfa di 0,05 e di una potenza di 0,80 di rilevare una differenza media di almeno 3,5 secondi nell'MCTt medio dopo il trattamento, presumendo una deviazione standard di 3,5 secondi sulla base dei risultati di studi pilota precedenti. Le variabili continue sono espresse come valori mediani e differenze interquartili, e le variabili categoriche come percentuali e numeri assoluti. Le differenze tra le misurazioni della pervietà nasale effettuate prima e dopo il trattamento sono state confrontate mediante il test chi quadrato o il test dei ranghi con segno di Wilcoxon per campioni appaiati, come opportuno. È stata calcolata anche la percentuale di partecipanti con effetti avversi imputabili al trattamento.

## **RISULTATI**

Tutti i soggetti hanno completato il trattamento senza segnalare effetti avversi.

Il test di Wilcoxon non ha rivelato alcuna differenza significativa nel flusso respiratorio nasale o resistenze nasali prima e dopo il trattamento, ma vi è stata una riduzione significativa dell'MCTt (Tab. 2). Diciotto dei 33 pazienti presentavano citologia nasale nella norma prima del trattamento, mentre 14 evidenziavano infiltrazione di cellule infiammatorie con (6) o senza la presenza di batteri (8); in un caso, l'esame citologico non è stato possibile perché il campione era insufficiente. La citologia nasale si è normalizzata dopo il trattamento nel 66% dei pazienti con reperti patologici al momento della prima valutazione (Tab. 3).

## DISCUSSIONE

Sebbene la frequenza di infiammazione/infezione delle vie aeree superiori abbia reso la congestione nasale un sintomo altamente prevalente, la rinite cronica, la rinosinusite, la poliposi nasale e il raffreddore comune sono spesso sottotrattati per via dell'efficacia o sicurezza spesso inadeguata delle terapie attuali [9,10]. Tuttavia, i risultati di alcuni studi pubblicati sembrano corroborare l'ipotesi che la crenoterapia inalatoria migliori i sintomi nasali, sebbene i meccanismi attraverso i quali ciò avviene siano ancora oggetto di dibattito.

Gli effetti terapeutici delle acque minerali dipendono dalle rispettive proprietà fisiche e chimiche. Studi precedenti hanno dimostrato gli effetti benefici dell'acqua solforosa sull'infiammazione cronica delle vie aeree e sulle secrezioni di muco: l'acqua agisce sulle mucoproteine rompendo i legami disolfuro e, di conseguenza, riduce la viscosità del muco [11,12]. La tossicità del solfuro fa sì che esso abbia anche effetti antibatterici [3,11]. Infine, esplica un'attività immunomodulatoria, poiché maggiori concentrazioni di IgA nel siero e nelle secrezioni, e ridotte concentrazioni di IgE nel siero, sono state osservate dopo la crenoterapia [13], e vi è una riduzione della conta dei neutrofili dopo il trattamento [3].

Abbiamo valutato la pervietà nasale di 33 pazienti dopo il trattamento inalatorio con acqua a base di oligominerali fluorurati radioattivi delle Terme Merano, osservando un miglioramento della funzione mucociliare: i valori mediani dell'MCTt patologici (valori di riferimento  $12,59 \pm 3$  min, in conformità a Passali *et al.*) [14] registrati all'inizio dello studio si sono ridotti a valori fisiologici dopo il trattamento.

Il trasporto mucociliare è un processo fisiologico, che consente al muco di scorrere sopra una lamina epiteliale di cellule ciliate, e rappresenta un importante meccanismo di difesa contro attacchi fisici e biologici nella fossa nasale, nei seni paranasali e nel tratto respiratorio inferiore. Le particelle e i microrganismi estranei inalati vengono catturati dal muco e trasportati verso la rinofaringe per mezzo dell'attività mucociliare nasale. Questo processo, che di solito impedisce a particelle organiche, inorganiche, batteriche o virali di entrare nell'organismo, ha un effetto protettivo sulle vie respiratorie superiori e inferiori. Nei pazienti che soffrono di infiammazione rinosinusale cronica, l'MCTt è ritardato

a causa di una riduzione dello strato periciliare e di un aumento della viscoelasticità del muco, provocati dal rilascio di mediatori infiammatori [14].

L'effetto positivo del trattamento con acqua radioattiva è stato dimostrato anche dal miglioramento nella rinocitogramma: il quadro citologico si è normalizzato dopo la terapia nel 66% dei pazienti che evidenziavano in precedenza infiltrazione di cellule infiammatorie nella mucosa (numero abnorme di neutrofili con o senza batteri).

Come dimostrato in altri studi [15], il trattamento con acqua a base di oligominerali fluorurati radioattivi ha un impatto positivo sulla funzione mucociliare e sul quadro citologico. Oltre alle azioni meccaniche aspecifiche di depurazione e drenaggio delle secrezioni, è possibile che la radioattività e gli ioni di fluoro contenuti in quest'acqua abbiano un effetto denaturante e antisettico su batteri, virus e allergeni, riducendo così il carico infiammatorio sulle mucose delle vie respiratorie. Data l'assenza di effetti indesiderati, il trattamento termale può offrire una scelta terapeutica alternativa in caso di malattie infiammatorie croniche delle vie aeree superiori che non rispondono al trattamento farmacologico.

**Tabella 1.** Composizione chimica essenziale delle acque delle Terme Merano (Merano, Bolzano, Italia).

<b>Parametro</b>	<b>Risultato</b>	<b>Unità di misura</b>
Pressione atmosferica	981	mbar
Temperatura aria	22	°C
Temperatura acqua	23.4	°C
Colore	incolore	
Odore	inodore	
Sapore	normale	
Sedimento	assente	
pH	7.48	u.pH
Conducibilità elettrica specifica	77	µS/cm
Durezza totale	3.2	°F
Alcalinità (espressa in CO <sub>3</sub> )	0	mg/L
Alcalinità (espressa in HCO <sub>3</sub> )	34	mg/L
Ossidabilità	<0.5	mg/L
Ammonio (espresso in NH <sub>4</sub> )	<0.02	mg/L
Nitriti (espressi in NO <sub>2</sub> )	<0.002	mg/L
Fluoruri	1.3	mg/L
Cloruri	<1.0	mg/L
Nitrati (espressi in NO <sub>3</sub> )	0.6	mg/L
Solfati	9	mg/L
Concentrazione di Radon in acqua	246	Bq/L



**Tabella 2.** Misurazioni AAR e MCTt prima e dopo la terapia inalatoria. La sigla “n” si riferisce al numero di casi validi per ciascuna variabile, e i dati vengono indicati come I quartile/valore mediano/III quartile. Il valore *p* si riferisce alla significatività della diversa distribuzione di ciascuna variabile prima e dopo la crenoterapia.

	<b>Prima</b>	<b>Dopo</b>	<b>p</b>
<b>Flusso respiratorio nasale</b>			
<b>Sinistro (n=64)</b>	252/332/460	250/388/506	0,532
<b>Destro (n=64)</b>	267/346/499	222/408/522	0,586
<b>Totale (n=65)</b>	512/672/912	580/740/1014	0,55
<b>Resistenza respiratoria nasale</b>			
<b>Sinistro (n=64)</b>	0,460/0,680/1,040	0,490/0,640/1,085	0,628
<b>Destro (n=63)</b>	0,485/0,615/1,012	0,430/0,690/0,975	0,839
<b>Totale (n=53)</b>	0,262/0,380/0,510	0,207/0,295/0,500	0,544
<b>Tempo di trasporto mucociliare (n=65)</b>	12/14/16	11/12/14	0,039

**Tabella 3.** Citologia nasale e presenza di batteri e funghi prima e dopo la terapia inalatoria. La sigla “n” si riferisce al numero di casi validi per ciascuna variabile, e i dati vengono indicati come percentuali, con numeri assoluti tra parentesi. Il valore *p* si riferisce alla significatività della diversa distribuzione di ciascuna variabile prima e dopo il trattamento con acqua termale.

	<b>Prima</b>	<b>Dopo</b>	<b>p</b>
<b>Cellule epiteliali (n=64)</b>			0,796
20-30	3%(1)	3%(1)	
60-70	3%(1)	0%(0)	
70-80	25%(8)	25%(8)	
80-90	69%(22)	72%(23)	
<b>Cellule calciformi (n=64)</b>			
05-10	12%(4)	6%(2)	0,16
10-20	12%(4)	31%(10)	
20-30	3%(1)	0%(0)	
30-40	72%(23)	62%(20)	
<b>Neutrofili (n=62)</b>			
0	10%(3)	16%(5)	0,288
1+	61%(19)	71%(22)	
2+	0%(0)	3%(1)	
3+	26%(8)	10%(3)	
4+	3%(1)	0%(0)	
<b>Eosinofili (n=62)</b>			
0	90%(28)	94%(29)	0,641
1+	10%(3)	6%(2)	
<b>Basofili (n=62)</b>			
0	100%(31)	100%(31)	
<b>Mastociti (n=62)</b>			
0	94%(29)	97%(30)	0,544
1+	6%(2)	3%(1)	
<b>Macrofagi (n=62)</b>			
0	100%(31)	97%(30)	0,313
1+	0%(0)	3%(1)	
<b>Linfociti (n=62)</b>			
0	97%(30)	97%(30)	1
1+	3%(1)	3%(1)	
<b>Plasmacellule (n=62)</b>			
0	100%(31)	100%(31)	
<b>Batteri (n=64)</b>			
0	81%(26)	91%(29)	0,5
1+	3%(1)	3%(1)	
3+	16%(5)	6%(2)	
<b>Miceti (n=64)</b>			
0	100%(32)	100%(32)	

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