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Effect of inhalation of thermal water on airway inflammation in chronic obstructive pulmonary disease

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Summary Thermal water inhalations have been traditionally used in the treatment of upper and lower chronic airway diseases. However, the benefit and the mechanism of this treatment have not been properly assessed.

To determine whether inhaled salt-bromide-iodine thermal water improves lung function, quality of life and airway inflammation, 39 patients with chronic obstructive pulmonary disease (COPD) were randomly assigned to receive 2-weeks inhalation treatment with thermal water (active, no. = 20) or normal saline (control, no. = 19) in single blind.

Lung volumes were measured, Saint George's respiratory questionnaire (SGRQ) was administered and induced sputum was performed before and after treatment.

No changes in pre- and post-salbutamol lung volumes was observed after inhalation treatment in both groups. SGRQ score showed a significant improvement in active group compared with control group at the end of the trial. The concentration of total cells in induced sputum increased significantly in both active ($P<0.05$) and control groups ($P<0.05$). Inhalation of thermal water induced a small but significant decrease in percentages of sputum neutrophils ($P<0.01$) and a parallel increase in macrophages ($P<0.01$). In contrast, normal saline inhalation was not associated with changes in differential sputum cell counts.

In conclusion, treatment with inhaled salt-bromide-iodine thermal water in COPD is associated with a reduced proportion of neutrophils in induced sputum suggesting

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that thermal water may have a mild anti-inflammatory effect on the airways. However, the short-term improvement in some components health-related quality of life was not related with changes in lung function or with the degree of airway inflammation.

Introduction

Chronic obstructive pulmonary disease (COPD) is clinically characterised by progressive airflow limitation often associated with excessive sputum production.[1,2] The inflammatory process implicated in COPD are detectable in different compartment of the airways and lung parenchyma.[3–7] Current treatment modalities for COPD are limited. These include symptom relief by bronchodilators. In addition, the appreciation that COPD is an inflammatory condition has led to manage the disease with agents that suppress the inflammation.[2] Inhalation of thermal water has been used empirically in the treatment of chronic diseases of upper and lower respiratory tract, including COPD. The benefit of thermal water has been attributed, at least partially, to its anti-inflammatory properties.[8,9] However, the type and degree of this activity on the airways of patients with COPD has not been performed by controlled studies. Analysis of induced sputum is a minimally invasive technique which has been used to directly evaluate airway inflammation in several clinical trials in COPD.[10] We specifically investigated whether a conventional course of inhaled salt-bromide-iodine thermal water would modify airway inflammation in patients with COPD treated for 2 weeks in a parallel-group randomized, placebo controlled study. Induced sputum was obtained from patients before and after treatment. Inflammatory cells and concentration of inflammatory mediators were examined in induced sputum. In addition, measurement of lung function, dyspnea and exercise tolerance, and health-related quality of life were performed.

Methods

Subjects and design of the study

We recruited 39 patients with stable COPD (35 men and 4 women, aged 44–76 years) from the outpatient department of University Hospital, Padova, and a local general practice. Inclusion criteria for entry were a smoking history of at least 10 pack-year, chronic bronchitis (a cough with excess of sputum production for at least 3 months in at least 2 consecutive years without any other disease)[1] or $FEV_1/FVC < 70\%$, and reversibility with inhaled salbutamol of $<15\%$ or 200 ml of initial FEV_1.[2] Patients with a history of asthma or atopy, or with other clinically significant diseases, and patients who had suffered a respiratory tract infection or exacerbation of their disease or had taken inhaled or systemic corticosteroids in the previous month were excluded. All subjects gave written informed consent, and the study was approved by the ethics committee of the University Hospital of Padova.

The patients were randomly assigned to receive 2-weeks inhalation treatment with thermal water (active group, no. = 20) or normal saline (control group, no. = 19) in single blind. Thermal water originated from hot springs (approximately 80 °C) in the Terme Euganee area (Abano-Montegrotto, Veneto, Italy). The main solutes in the water are Br (13.6 g/l), Cl (2.2 g/l), Na (1.2 g/l), SO_4 (1.0 g/l), I (0.8 g/l), Ca (0.4 g/l). Thermal water was free from bacterial contamination, had a pH = 7.1 and osmolarity of 124 mmol/l.

Thermal water or sterile normal saline solution were warmed up at a temperature of approximately 37 °C and nebulised. The aerosols were administered once a day for 20 min. Each subject was examined twice, before and after the 2-weeks treatment. Each visit included the evaluation of health-related quality of life using the Italian version of the St. George's respiratory questionnaire (SGRQ),[11] pulmonary function tests, a 6-min walking test and sputum induction.

Pulmonary function tests

Pulmonary function tests were performed with a spirometer (Biomedin, Padova, Italy) as previously described[12] and included the measurements of FEV_1 and FVC before and 15 min after inhalation of 200 μg of salbutamol. Subjects were tested at least 12 h after the last inhaled bronchodilator. The predicted normal values were those from Communitè Europèenne du Carbon e de l'Acier (CECA).[13]

Six minutes walking test

Subjects were instructed to walk as far as they could for 6 min along a 32 m corridor.[14] Before and after the test arterial oxygen saturation and heart

rate were assessed with finger pulse-oximeter (Onyx 9500 Oximeter, Nonin Medical Inc., Minneapolis, USA). Walk distance in meters and dispnea according to Borg scale were evaluated at the end of the test.

Sputum induction and analysis

Sputum was induced by inhalation of hypertonic saline as described.[12] Briefly, FEV_1 was measured before and 10 min after salbutamol inhalation (200 μg). Hypertonic saline was nebulised with an ultrasonic nebuliser (Ultra Neb 2000, De Vilbiss Health Care, Somerset, PA, USA) for 5 min periods, up to 20 min. The concentration of saline was increased at intervals of 10 min from 3% to 4%. Each 5 min subjects were asked to rinse their mouths and throats and then invited to cough sputum into a Petri dish. Sputum plugs arising from the lower respiratory tract were selected and gently mixed with dithiothreithol 0.1% (Sputasol; Oxoid Ltd., Basingstoke, England). The supernatant was separated and aliquots were kept frozen at −80 °C until analysed. The cell suspension was spun in a cytocentrifuge (Shandon Cytospin2; Shandon, Oakland, CA), and the slides were stained with Diff Quick for differential cell counts of leukocytes and squamous epithelial cells. The slides were coded and 400 cells were counted blindly for differential leukocyte count. A sample was considered adequate when the percentage of squamous cells was lower than 20%. To correct for the variable salivary contamination, the results of differential leukocytes counts were expressed as a percentage of nucleated cells excluding squamous cells.

Myeloperoxidase (MPO) concentrations in sputum supernatant were determined with a commercially available radioimmunoassay (Pharmacia Diagnostics AB, Uppsala, Sweden) according to the manufacturer's instructions.

Eosinophils cationic protein (ECP) concentrations were measured using anti-ECP monoclonal antibody coupled to ImmunoCAP according to the manufacturer's instructions (Pharmacia Diagnostics).

Data analysis

Group data were expressed as means ± standard error or median and interquartile ranges. The comparison of the results was made using Mann–Whitney *U* test or the Wilcoxon's rank sum test. The relationship between sputum cytology results and SGRQ scores was evaluated with the Spearman rank correlation test. The significance was accepted at the 5% level.

Results

The baseline characteristics of the patients are shown in Table 1. According to the GOLD classification of severity 16 patients were at stage 0, 9 at stage I, 3 at stage II, 10 at stage III, and 1 at stage IV.[2] The two groups were similar with regard to age, sex, smoking history, pulmonary function tests and overall severity of the disease. No COPD exacerbation occurred during the course of the study and inhaled treatments were well tolerated.

A significant reduction of the SGRQ total score was observed after thermal water treatment indicating an improvement of health related quality of life (Table 2). The improvement in active group regarded the Activity and Impact sections. In contrast, no changes in SGRQ scores was detected in control group.

There was no significant change in lung function indices after control or thermal water treatment periods. Similarly, no differences were detected in walk distance, post-exercise arterial oxygen saturation and dyspnea score measured during the

Table 1 Baseline characteristics of patients in each treatment group.

	Control ($n = 19$)	Thermal water ($n = 20$)
Sex (M/F)	16/3	19/1
Age (yr)	65 ± 2	63 ± 2
Smoking history (pack-yr)	33 ± 3	35 ± 4
FEV_1 (% predicted)	71 ± 6	73 ± 5
FEV_1/FVC%	62 ± 2	69 ± 3
Post-bronchodilator FEV_1 (% baseline)	6 ± 1	5 ± 1
Arterial oxygen saturation (%)	95 ± 0.4	95 ± 0.4
Dyspnea score (Borg scale)	0.7 ± 0.1	0.7 ± 0.1

Data are expressed as mean ± SE.

Table 2 Changes in health-related quality of life assessed by St. George's respiratory questionnaire before and after treatment with inhaled normal saline (control) and thermal water.

SGRQ score	Control		Thermal water	
	Baseline	After treatment	Baseline	After treatment
Symptoms (1–100)	41 ± 5	43 ± 5	36 ± 4	32 ± 4
Activity (1–100)	44 ± 5	48 ± 5	40 ± 4	29 ± 4*
Impact (1–100)	26 ± 4	33 ± 4	18 ± 4	14 ± 3*
Total score (1–100)	34 ± 3	38 ± 4	28 ± 3	22 ± 3*

Data are expressed as mean ± SE.
*$P < 0.01$ compared with corresponding values in control group (Mann–Whitney test).

6-min walk test. The proportion of patients who increased the walking distance of more than 30 m was higher in active treatment ($n = 8$, 40%) than in control ($n = 4$, 21%), but the difference was not statistically significant. Subgroup analysis performed excluding the subjects with FEV_1/FVC > 70% did not show significant differences in FEV_1 (change after treatment: thermal water 1.6 ± 1.6%; control 0.7 ± 1.3%) or walk distance (change after treatment: thermal water 22 ± 20 m; control 13 ± 7 m) in subjects with mild to severe COPD.

The induction of sputum was well tolerated and all patients produced adequate samples. The amount of sputum plugs collected before treatment was similar in the two groups (control median 210 mg [interquartile range 132–246]; thermal water 216 mg [139–276]) and did not change from baseline on control (240 mg [136–262]) or active (205 [160–286]) treatment. A significant increase in the total cell number was observed in either groups after treatment (Table 3).

The percentage of sputum neutrophils significantly decreased after treatment with inhaled thermal water compared with pre-treatment values, while the percentage of macrophages increased. The observed changes were small, but consistent among patients (Fig. 1). Differential cell counts did not change from baseline on control treatment (Table 3). Similarly, the concentrations of MPO and ECP remained unchanged throughout the study in both groups. No correlation was detected between SGRQ and lung function or sputum indices.

Discussion

This is the first controlled study to examine the effect of a standard course of inhaled salt-bromide-iodine thermal water on respiratory function and airway inflammation in COPD. We showed that the active treatment was associated with a short-term improvement in health-related quality of life without changes in lung volumes, arterial oxygen saturation or exercise capacity. The reduction in the proportion of sputum neutrophils detected at the end of the course of thermal water inhalation might be regarded as a mild anti-inflammatory effect of salt-bromide-iodine thermal water on the airways in COPD. However, it appears insufficient to explain the benefit of thermal water on health status perception. Larger studies may be necessary to confirm these observations.

COPD is characterised by airflow limitation. Some components of the functional impairment may be partially reversible.[2] It was hypothesised that thermal water could act on these components by reducing inflammation and/or modifying mucous properties. Reduction of mucus in the lumen of the airways or of inflammatory infiltrate in the airway wall would result in higher expiratory flows. Improved accessibility of inhaled drugs to airway smooth muscle would increase post-bronchodilator FEV_1. Finally, better lung distribution of ventilation would improve exercise capacity of the subjects. None of these effects had been demonstrated in our study. The inclusion in the trial of patients with insufficiently severe disease might have prevented the detection of treatment effects on lung function. Subgroup analysis performed excluding the subjects at risk (stage 0) according to GOLD classification, apparently did not confirm this hypothesis, since no different outcome was observed in subjects with mild to severe COPD. However, we need to be cautious with this interpretation, since the lower number of subjects in subgroups reduces the power of statistics. Different individual response to treatment is a common problem in clinical trials. A cross-over design of the study could have reduced the

Table 3 Inflammatory indices in induced sputum before and after treatment with inhaled normal saline (control) and thermal water.

Induced sputum	Control		Thermal water	
	Baseline	After treatment	Baseline	After treatment
Total cell count/mg (no.)	1776 (1104–2591)	2700* (2161–3958)	2881 (1655–4786)	2964* (1944–9218)
Viability (%)	92 (89–98)	91 (88–94)	92 (90–94)	90 (85–95)
Differential cell count				
Macrophages (%)	38.2 (27–52)	35.5 (26–54)	34.1 (22–49)	37.6* (29–52)
Neutrophils (%)	61.6 (48–72)	65.1 (55–77)	64.3 (50–78)	61.8* (47–71)
Eosinophils (%)	0.3 (0.1–0.8)	0.0 (0.0–0.8)	0.3 (0.0–0.2)	0.3 (0.0–0.0)
Lymphocytes (%)	0.0 (0.0–0.2)	0.0 (0.0–0.1)	0.0 (0.0–0.4)	0.0 (0.0–0.1)
Sputum supernatant				
MPO (ng/ml)	194 (89–380)	217 (20–522)	200 (46–335)	233 (39–555)
ECP (ng/ml)	95 (61–200)	80 (54–200)	59 (27–150)	57 (20–131)

Data are expressed as median (interquartile range).
*$P<0.01$ compared with corresponding baseline values (Wilcoxon signed rank test). MPO = myeloperoxidase; ECP = eosinophil cationic protein.

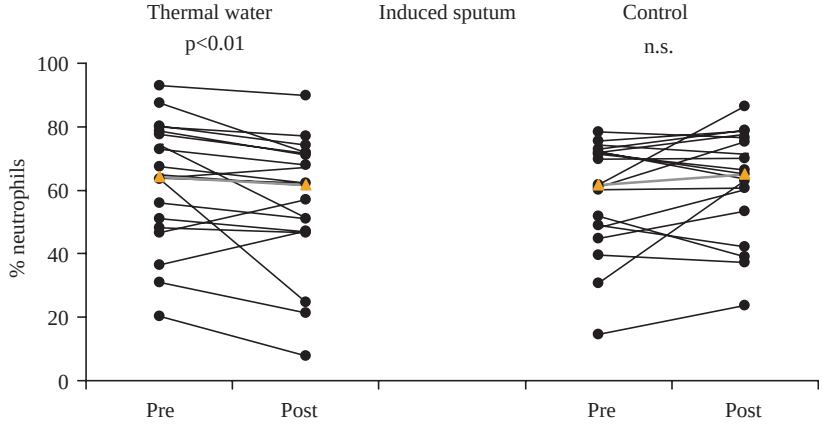

Figure 1 Individual percentages of sputum neutrophils before and after treatment with inhaled thermal water and normal saline (control).

influence of individual variability. However, we chose a parallel group study design because it is unknown if there is any carry over effect of inhalations.

The hypothesis that thermal water had anti-inflammatory properties was based on few previous studies performed in patients with rhinitis. Treatment with sulphurous thermal water resulted in a reduction of polymorphonuclar cells in nasal cytology of patients with chronic inflammation of upper respiratory tract.[8] Improvement of symptoms, decrease in serum IgE and increase in serum IgA was observed in patients with perennial allergic rhinitis after treatment with iodine bromide thermal water.[9] However, no investigations were performed in lower respiratory tract. The decrease in sputum neutrophils is consistent with the observation made in nasal cytology after inhalation

of a different thermal water. Neutrophilia is the predominant feature of intraluminal airway inflammation in COPD[15–17] and percentages of sputum neutrophils correlated with accelerated decline of FEV_1 over 15 years.[5] For these reasons treatments aimed to reduce airway neutrophilia should be regarded as beneficial. Most of current treatment modalities for COPD have no or controversial effects on the inflammatory process. Two studies in patients with COPD have reported a reduction in sputum neutrophils after inhaled corticosteroids,[18,19] but these results were at variance of further reports.[20,21] A reduction in sputum neutrophils has been demonstrated after treatment with theophylline,[22] but a trial with a more specific phosphodiesterase-4 inhibitor failed to show changes in sputum inflammatory cells.[23] The neutrophil decrease detected after inhaled thermal water was consistently homogeneous. However, the size of neutrophil reduction was minimal and at the end of the trial the subjects retained their characteristic neutrophilic inflammation. Since our study was designed to investigate the effects of conventional course of inhaled thermal water, it cannot be ruled out that higher doses or more prolonged periods of treatment might be applied to obtain more relevant results.

The increased recovery of cells in induced sputum observed after both treatments is consistent with the observations made in COPD patients that inhalation of isotonic or hypertonic solutions administered by nebulisation induce increase in airway secretion that can be expectorated.[24,25] The mechanisms by which this occur are not known[26] and the present study was not designed for mechanistic investigation. Inflammatory mediator release has been shown after exposure of human airways to hyperosmolar solutions.[27] In contrast, we did not observe any alteration of the secretory profile of sputum granulocytes. Previous reports have demonstrated increased clearance of secretions from the airways in humans after administration of hypertonic saline aerosols.[28] However, since the increase in sputum leucocytes was irrespective of the type of solution administered to our patients, our findings suggest that the amount of fluid deposited the airways favours the recovery of cells rather than the properties of the solutes. Indeed, hydration has been used empirically in chest physical therapy, and there is some objective evidence in animal model that hydration increase tracheal mucus transport velocity.[29]

The SGRQ resulted a sensitive method to detect changes in health status of our COPD patients. We provide evidence of some benefit of a course of inhalation of thermal water in COPD. Active treatment significantly improved the activity and impact domains, but not symptoms. This is in line with the lack of functional changes detected in the patients. Otherwise, it is not clear which effect of thermal water is responsible of such improvement since no correlation was detected with questionnaire scores or indices of pulmonary function or airway inflammation. One possible explanation of the positive effect on quality of life could be that some patients recognised the inhalation of thermal water due to a different taste. Unblinded patients could have been influenced by the common opinion on the efficacy of thermal water to give more favourable answers in the activity and impact domains of SGRQ.

In summary, we have shown that treatment with inhaled salt-bromide-iodine thermal water in COPD is associated with a reduced proportion of neutrophils in induced sputum suggesting that thermal water may have a mild anti-inflammatory effect on the airways. However, the short-term improvement in some components health-related quality of life was not related with changes in lung function or with the degree of airway inflammation. Thermal water is not considered in the treatment of COPD suggested by the most recent guidelines.[2] Our data do not provide sufficient evidence that a short course of inhaled thermal water in COPD patients has clinically relevant benefit to be included in the standard management of COPD.

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