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Halotherapy as Asthma Treatment in Children: A Randomized, Controlled, Prospective Pilot Study

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Summary. Background and Objectives: Asthma is a chronic inflammatory disorder requiring intermittent or continuous anti-inflammatory therapy. Patients often turn to alternative treatments as complements or replacements to conventional treatments. We aimed to evaluate the effect of salt room chambers (halotherapy) on bronchial hyper-responsiveness (BHR), fractional exhaled nitric oxide (FeNO), and quality of life in children with asthma. Patients and Methods: Children aged 5–13 years with a clinical diagnosis of mild asthma not receiving anti-inflammatory therapy. Patients were randomized in this double-blind, controlled study to salt room with halogenerator (treatment group), or without halogenerator (control group). We evaluated the effect of salt room therapy on BHR, FeNO, spirometry, and pediatric asthma quality of life questionnaire (PAQLQ). The treatment period lasted 7 weeks, 14 sessions. Results: Twenty-nine patients were randomized to the salt room with halogenerator (treatment group), and 26 patients to the salt room without salt halogenerator (control group). A statistically significant improvement in BHR was demonstrated in the treatment group, which remained unchanged in the control group. There was no improvement in spirometry or FeNO levels following treatment. The treatment group showed a statistical improvement in most parameters of quality of life questionnaires. Conclusions: Our pilot study suggests that salt room with halogenerator, may have some beneficial effects in mild asthmatic children. Randomized and larger controlled trials with long-term follow-up are necessary. **Pediatr Pulmonol. 2017;52:580–587.**

Key words: asthma; halotherapy; airway hyper-reactivity; metacholine challenge test; fractional exhaled nitric oxide.

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INTRODUCTION

Asthma is a chronic inflammatory disorder associated with bronchial hyper-responsiveness (BHR). Treatments including β2 receptor agonists and anti-inflammatory drugs (inhaled corticosteroids or leukotriene receptor antagonist) have been recommended for children at risk for asthma exacerbations. Clinically, meaningful improvements in the control of asthma and in airway responsiveness are achieved during continuous treatment but do not persist after treatment is discontinued.[1] The chronic nature of the disease and parental concerns regarding possible side effects result in low adherence rates and a search for alternative treatments as complementary or replacements to conventional treatments.[2–4]

Salt therapy (halotherapy, derived from the Greek *halos* = salt, and speleotherapy derived from the Greek *speleos* = cave), has been practiced in Central and Eastern Europe for centuries. Speleotherapy is claimed to provide several advantages, such as absence of normal biotic conditions (e.g., light), temperature difference between earth surface and underground, natural (but higher than normal) radiation level, presence of mineral water, drops of several minerals. Halotherpy consists of sitting in a room coated with salt crystals and pumped with salt-laden air from a halogenerator. The experience is designed to

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Conflicts of interest: None.

Clinical Trial Registration: NCT02772341.

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mimic some, but not all, the benefits of the microclimate of natural salt caves in Eastern Europe. To the best of our knowledge, only one double-blind controlled study (in adults) assessed the role of halotherapy in asthma.[5]

In spite of paucity of evidence of a beneficial effect, an increasing number of asthmatic children are treated by complementary and alternative medicine, such as salt rooms. Our hypothesis was that there would be no objective benefit to salt room therapy in asthma. The aim of this double-blind controlled trial was to evaluate objectively the efficacy of halotherapy in children with asthma.

PATIENTS AND METHODS

The study was approved by the institutional review board of Rambam Health Care Campus (#0059-12). Consecutive children referred to the Pulmonary Outpatient Clinic of a tertiary university-affiliated medical center who met inclusion criteria were included in the study. Inclusion criteria were age 5–13 years, clinical diagnosis of mild asthma, and a positive methacholine challenge test (methacholine provocation concentration causing 20% reduction in FEV_1 (PC_{20}-FEV_1) <16 mg/ml).[6]

Exclusion criteria were: $FEV_1 < 65\%$ predicted; an acute illness on the day of the MCT; anti-inflammatory treatment over the past 14 days; administration of β2 agonists over the previous 24 hr; oral corticosteroids, emergency room (ER) visit, or hospital admission for respiratory symptoms over the past 2-months; or previous halotherapy treatment.

Methods

Study Design

The study was a randomized, double-blind, controlled study, and included two visits.

Visit 1. Written parental consent was obtained. Demographic data, child's history of asthma and atopy history, and family history of asthma, atopy, and smoking were recorded. The Pediatric asthma quality of life questionnaire (PAQLQ) was completed by the patient/caregiver and the interviewer. Each patient performed spirometry, MCT, and FeNO measurements. Following a positive MCT, patients were randomized to 14 sessions (7 weeks, twice weekly, 45 min each treatment) sitting in a salt room with salt aerosol produced by a halogenerator (treatment group) or halotherapy without salt aerosol (control group). Randomization was carried out solely by the salt room personnel in blocks of 10 (five children to treatment and five to control). Both the walls and the ceiling of the salt room are completely covered with ESCO-(European Salt Company) type certified-origin rock salt. The temperature (20–24°C) and humidity (44–60%) are at constant values. The halogenerator is located outside the salt room. The same salt room was used for both the halotherapy treatment arm and the control arm. In the treatment group, dry NaCl particles (~20 μm) were blown into the salt room while the blower was working without NaCl in the control group. The patients were instructed to use inhaled β2 agonists as needed and to report any asthma exacerbation, use of medication, or health care visit.

Visit 2. After 7 weeks, each patient underwent a second evaluation by spirometry, MCT, FeNO, and PAQLQ. The research team (respiratory technicians and physicians) were blinded to the allocation until the final statistical analysis was done.

Asthma exacerbation was defined as any use of anti-inflammatory treatment (oral corticosteroids or inhaled corticosteroids/oral montelukast) or inhaled β2 agonist treatment for longer than 3 days consecutively.

Medical indication to withdraw from the study included: asthma exacerbation treated with inhaled steroids/oral montelukast >7 days or any dose of systemic steroids, hospitalization (any diagnosis). These criteria were used to ensure the safety of patients in an unproven treatment and to avoid possible attenuation of MCT challenge by the treatment.

Additionally, any administration of anti-inflammatory drugs during the 2 weeks prior to evaluation was considered as an indication not to proceed with MCT.

Spirometry

Spirometry was performed in accordance with the ATS/ERS (American Thoracic Society/European Respiratory Society) Task Force, using a KoKo spirometer (nSpire Healthcare Inc., Longmont, CO).[7] Results were expressed as percent predicted derived from Quanjer.[6]

Methacholine Challenge Test (MCT)

MCT was performed according to published guidelines.[8]The solutions were administered using a pulmonary dosimeter (nSpire Healthcare, Inc.) according to manufacturer's instructions. On completion of MCT, 200 mcg of albuterol inhaler was given to all patients.

Fractional Exhaled Nitric Oxide (FeNO)

Patients performed three online single breath maneuvers according to international guidelines using the Eco Medics NO-analyzer (CLD 88 exhalyzer Eco Physics AG, Duernten, Switzerland). An animation biofeedback assisted the children in maintaining the flow rate at 50 ml/sec during the total length of the exhalation.[9] The mean value of at least two successful FeNO measurements, according to ATS/ERS guidelines, was entered in the analysis.

PAQLQ

A Hebrew version of the Standardized Pediatric Asthma Quality of Life Questionnaire is a validated instrument that evaluates overall QOL of childhood asthma and the impact that the child's asthma has on the primary caregiver's day-to-day experiences through its different subdomains (symptoms, activity limitation, and emotional). Each question is rated on a 7-point scale (from 1 = severe impairment to 7 = no impairment).[10] The patient/caregiver and the interviewer completed the questionnaires at baseline and at the end of the study. The same parent and the same interviewer completed the questionnaires at the two visits.

ANALYSIS AND STATISTICS

Primary Outcome

PC_{20}-FEV_1.

Secondary Outcomes

Spirometry, Fractional exhaled NO (FeNO), PAQLQ.

Statistical analysis was performed using a software package (SPSS, version 21; SPSS Inc., Chicago, IL). All data were expressed as mean, STD, median, percentiles, and 95% confidence intervals (95% CI). Kolmogorov–Smirnov test was used to evaluate the distribution of the quantitative parameters. As some of the quantitative parameters were not normally distributed, a non-parametric test was applied. Differences between the two groups (treatment vs. control) in the quantitative parameters were demonstrated by *t*-test or Mann–Whitney whenever needed.

Fisher exact test and Pearson chi square were used for differences in participant characteristics between the two groups.

PC_{20} was logarithmically transformed for analysis and reported as the geometric mean. The paired *t*-test and repeated measures model were used to compare pre- versus post-measurements for FEV_1, FeNO, FEF 25–75 parameters results.

$P < 0.05$ was considered as significant.

Power Calculation

A clinically relevant difference in PC_{20} was assumed to be at least 1.0 mg/ml, and SD 1.3 with an α of 0.05 and a β of 0.2, indicating that we would need at least 27 children per group. With a drop-out rate of 15%, the number of children per group needed to be $\geq$31.

RESULTS

As shown in Figure 1, 60 children were enrolled in the study. One child failed to meet the inclusion criteria (MCT > 16 mg/ml) and 59 children with positive MCT entered the study. Three children were excluded, two due to parental logistic reasons, and one due to respiratory exacerbation before randomization. A total of 56 patients were randomized, 27 to control and 29 to the treatment group. Four randomized patients did not complete the study. One patient was excluded from analysis due to inconsistent recordings of type of room assignment and suspected neurological tics. The other three patients, two in the control group and one in the treatment group, did not complete the study due to: parental logistic reasons, claustrophobic reaction, asthma exacerbation, respectively. Therefore, 24 patients in the control group and 28 in the treatment group completed the study. When asking the patients a direct question, none of them could tell if dry salt aerosol was generated by halogenerator or not.

Asthma exacerbations were reported in five patients; three in the treatment group and two in the control group. Four patients were treated $\geq$3 days with inhaled bronchodilators and just one patient (treatment group) had to use inhaled steroids.

Patients' characteristics are presented in Table 1. As can be seen, the two groups were similar at baseline with regard to all baseline characteristics.

Table 2 shows baseline spirometry, PC_{20} concentration, stage, and FENO before and after treatment in the two

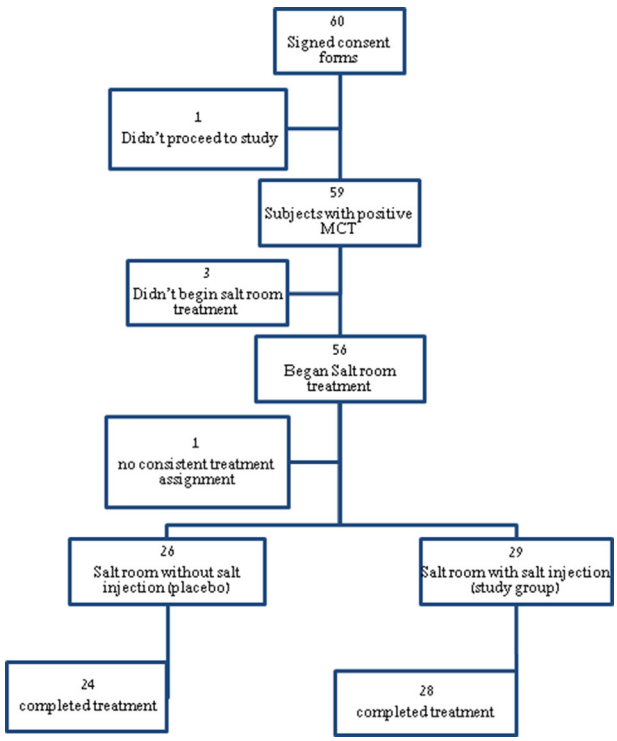

Fig. 1. Flow of participants in the study.

TABLE 1— Study Population Characteristics

Parameter	Salt room without halogenerator	Salt room with halogenerator	*P*-value
Patients	27 (47%)	30 (53%)	NS
Sex (M)	17 (63%)	19 (63%)	NS
Age (years)	8.2 ± 2.4	9.2 ± 2.5	NS
Allergic rhinitis	13 (48%)	16 (53%)	NS
Atopic dermatitis	6 (22%)	5 (16.7%)	NS
Passive smoking	8 (30%)	12 (40%)	NS
Pets (feline/canine)	2 (7.4%)	8 (26.7%)	NS
Allergy skin test	11/19 (57.9%)	12/23 (52.2%)	NS
Wheezing	19 (70.4%)	27 (90.0%)	NS
Dyspnea	20 (74.1%)	26 (86.7%)	NS
Nocturnal complaints	16 (59.3%)	13 (43.3%)	NS
Effort dyspnea	17 (63.0%)	26 (86.7%)	NS
Past treatment	23 (85.2%)	26 (86.7%)	NS
Hospitalizations for asthma	5 (18.5%)	5 (17.2%)	NS

groups. A statistically significant improvement in BHR (PC_{20} concentration and Stage of PC_{20}) was demonstrated in the treatment group, while no change was observed in the control group (Fig. 2A and B). As can be seen, some patients in the treatment group responded by more than two doubling doses. There was no change in FeNO levels and no improvement in spirometry following treatment in either group. Some of spirometric parameters decreased in the two groups of patients (salt room with and without halogenerator). Tables 3 and 4 show the quality of life questionnaire scale (self-administered and by interviewer, respectively) before and after treatment in the two groups. There was a statistical improvement in most parameters of the self-administered quality of life questionnaires and in all parameters of the interviewer-administered questionnaires in the treatment group, while these parameters remained unchanged in the control group. There was no seasonal variation in the response of the parameters evaluated to salt room.

DISCUSSION

This double-blind controlled study evaluated the effect of salt room chambers with and without halogenerator on BHR assessed by MCT, FeNO, and quality of life during the 7 weeks of the study period. The study showed a statistically significant improvement in BHR and in most parameters of quality of life questionnaires in children assigned to salt room therapy with halogenerator. These parameters remained unchanged in the control group. There was no improvement in spirometry or FeNO levels following treatment.

Salt therapy centers are emerging as a treatment option in the USA, Western Europe, and Canada. Although there

TABLE 2— Baseline Spirometry, PC20 Concentration, Stage, and FENO Before and After Treatment in the Two Groups

	Salt room without halogenerator, n = 24		Salt room with halogenerator, n = 28		
Parameter	Before treatment	After treatment	Before treatment	Before treatment	*P*-value
PC_{20} (mg/ml) mean ± SD	2.61 ± 3.35	2.24 ± 2.75	2.23 ± 3.12224	6.41 ± 7.36	NS[1], 0.044[2], NS[3], 0.012[4]
PC_{20} (mg/ml) median(range)	1.64 (0.16–2.87)	0.89 (0.10–3.61)	0.96 (0.11–3.43)	2.62 (0.32–16)	NS[1], 0.044[2], NS[3], [4]0.012[4]
Stage of PC_{20}*	4.1 ± 1.6	3.9 ± 1.8	3.7 ± 1.6	4.7 ± 2.1	NS[1], 0.04[2], NS[3], NS[4]
FeNO (ppb) mean ± SD	22.01 ± 18.39	28.97 ± 31.03	35.49 ± 37.79	38.16 ± 35.05	NS[1], NS[2], NS[3], NS[4]
FeNO (ppb) median(range)	16.7 (6.3–36.1)	20.6 (11.7–36.8)	20.55 (9.1–38.8)	22.05 (12.4–59.1)	NS[1], NS[2],NS[3], NS[4]
FEV_1 (L/sec)	1.6 ± 0.52	1.54 ± 0.48	1.80 ± 0.38	1.77 ± 0.39	NS[1], NS[2], NS[3], NS[4]
FEV_1 (%predicted)	86.4 ± 9.5	81.8 ± 12.3	91.2 ± 12.7	86.1 ± 11.9	0.003[1],0.003[2], NS[3],NS[4]
FEV_1/FVC	0.87 ± 0.08	0.85 ± 0.08	0.87 ± 0.07	0.85 ± 0.07	0.009[1], NS[2],NS[3],NS[4]
FEV_1/FVC (%predicted)	102.2 ± 9.4	98.3 ± 9.8	101.2 ± 8.6	99.4 ± 8.4	0.008[1], NS[2],NS[3],NS[4]
$FEF_{25–75}$ (L)	1.79 ± 0.54	1.60 ± 0.51	2.01 ± 0.58	1.97 ± 0.63	0.017[1],NS[2],NS[3],0.032[4]
$FEF_{25–75}$ (%predicted)	79.6 ± 18.4	70.5 ± 20.3	83.1 ± 18.9	78.41 ± 21.4	0.007[1], 0.046[2], NS[3],NS[4]

[1]Placebo group: between baseline versus after treatment.
[2]Treatment group: between baselines versus after treatment.
[3]Baseline time: placebo versus treatment groups.
[4]After treatment: placebo versus treatment groups.
*Stage of PC20—the stage in the sequence of doubling doses in the MCT test.

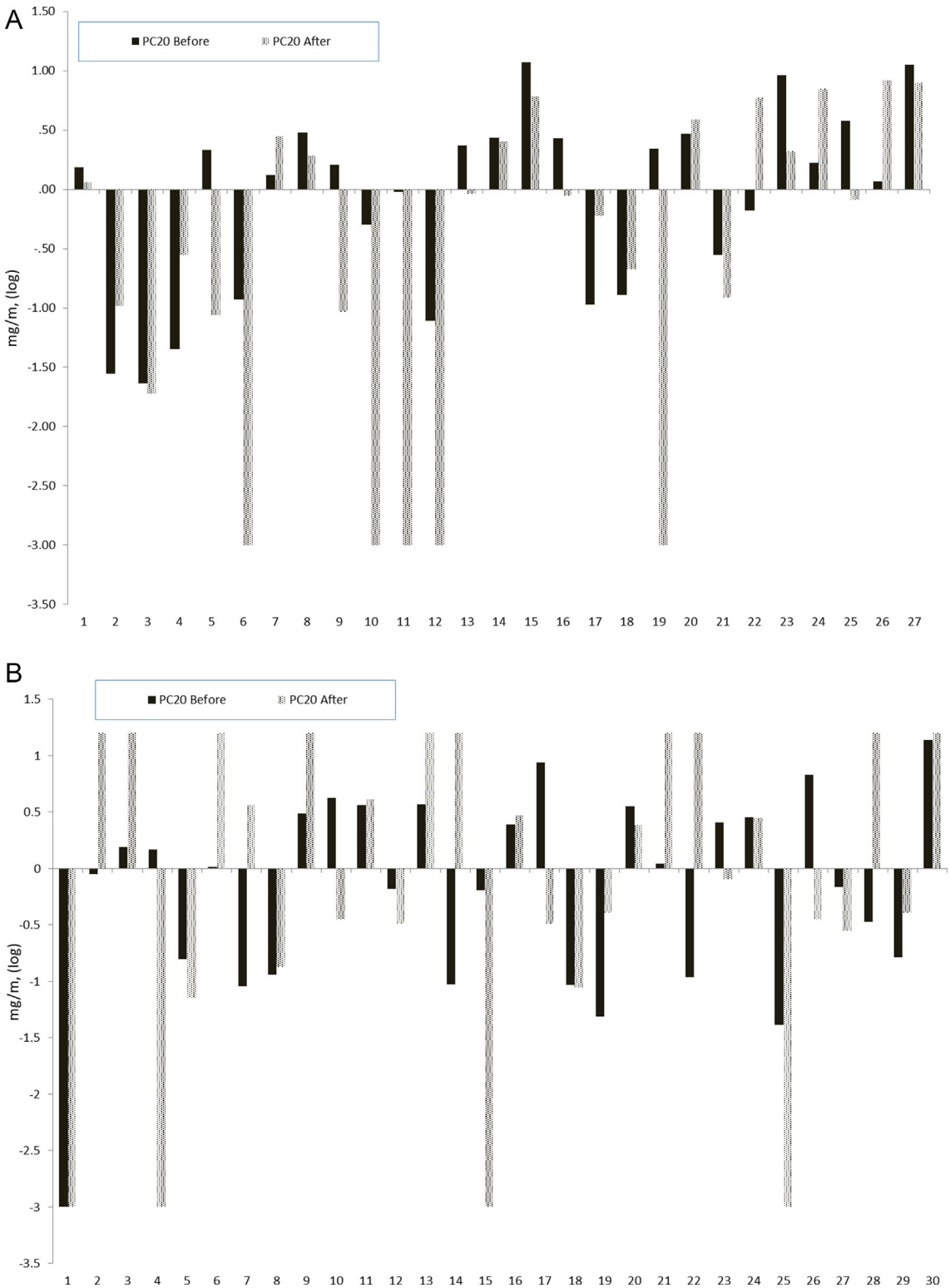

Fig. 2. A: Individual change in MCT values of patients in the control group. B: Individual change in MCT values of patients in the treatment group.

is a paucity of clinical trials to evaluate their efficacy, parents are willing to invest time and money in salt rooms with their asthmatic children. When visiting pulmonary clinics, parents often ask their physicians regarding the safety and efficacy of salt rooms. The answer that could be given is that there is no data to support this treatment. The lack of data regarding safety and efficacy of a type of treatment gaining increasing popularity led us to conduct

TABLE 3—Self-Administered Quality of Life Questionnaires for Asthma Patients PAQLQ(S) Before and After Salt Room With/Without Halogenerator

	Salt room without halogenerator, n = 23		Salt room with halogenerator, n = 21	
Parameter	Before treatment	After treatment	Before treatment	After treatment
Symptoms	6.47 ± 0.16	6.27 ± 0.98	6.32 ± 0.84	6.78 ± 0.32
	NS		$P = 0.016$	
Activity limitation	6.0 ± 1.33	6.09 ± 1.33	5.85 ± 1.18	6.35 ± 0.75
	NS		NS ($P = 0.051$)	
Emotional function	6.58 ± 0.81	6.65 ± 0.82	6.5 ± 0.69	6.85 ± 0.3
	NS		$P = 0.007$	
Weighted average	6.4 ± 0.74	6.36 ± 0.89	6.29 ± 0.76	6.71 ± 0.33
	NS		$P = 0.004$	

Values presented as mean ± SD. n = 21.

the study. We chose to evaluate children with mild asthma not receiving anti-inflammatory agents (either because they had mild intermittent episodes or because of parental refusal to give daily treatment). This group allowed us to evaluate an unproven therapy without denying any indicated care. We evaluated multiple objective parameters. Asthma symptoms and exacerbations were not chosen, as these were mildly asthmatic children with few exacerbations and few daily symptoms.

Our primary outcome was defined as BHR assessed by MCT. Increased sensitivity to bronchoconstriction with provocative agents, including methacholine, is a fundamental pathophysiological mechanism associated with symptomatic asthma and may be an indicator of unremitting asthma. Improvement of airway reactivity is considered as a dimension of therapeutic response in asthma and can be considered a valid proof of concept for a treatment.[11] We chose MCT (a direct bronchoconstriction stimulus) which is a sensitive test used in clinical work, although an adenosine (a potent indirect bronchoconstriction enhancing the release of mediators from mast cells) challenge test may be more specific.[12] The study showed a significant increase in both MCT concentration and the stage required to achieve PC_{20} in the treatment group. Of note, some of the patients had improvement in PC_{20}, similar to that achieved by inhaled corticosteroids[13] and some had a negative MCT following treatment. It has been previously reported that 23% of patients with physician-diagnosed asthma on active controller treatment have a negative MCT.[14]

The recruitment was conducted over a whole year, and improvement was not seasonally dependent.[15] Our results are in line with the single double-blind controlled study that evaluated the effect of a salt chamber as add-on therapy on bronchial reactivity to a histamine challenge in adults and demonstrated a similar reduction in bronchial hyperresponsiveness.[5]

As opposed to MCT, there was no positive effect on spirometry, although some spirometric indices statistically decreased. As can be seen, the fall in lung function was not consistent. Some parameters did not decrease in absolute values, but reached statistical difference in % predicted. It should be noted that we included children with mild asthma with no room for improvement in

TABLE 4—Interviewer Administered Quality of Life Questionnaires for Asthma Patients PAQLQ(S) Before and After Salt Injection/Placebo

	Salt room without halogenerator, n = 23		Salt room with halogenerator, n = 28	
Parameter	Before treatment	After treatment	Before treatment	After treatment
Symptoms	6.59 ± 0.46	6.56 ± 0.61	6.5 ± 0.69	6.7 ± 0.65
	NS		$P = 0.029$	
Activity limitation	6.58 ± 0.53	6.68 ± 0.51	6.21 ± 0.86	6.49 ± 0.8
	NS		$P = 0.017$	
Emotional function	6.78 ± 0.47	6.83 ± 0.28	6.61 ± 0.58	6.89 ± 0.21
	NS		$P = 0.006$	
Weighted average	6.65 ± 0.49	6.68 ± 0.39	6.46 ± 0.64	6.72 ± 0.47
	NS		$P = 0.012$	

Values are presented as mean ± SD.

spirometry. We assessed FeNO, a measure of eosinophilic inflammation. The values did not change following salt room chamber therapy. One previous study assessed the effect of a salt chamber on induced sputum eosinophilic cationic protein,[16] and concluded that the reduction in hyper-responsiveness was probably not due to the effect on eosinophilic inflammation.

Our speculation was that breathing salt may worsen asthma in some patients by irritating and constricting the airways, and by engaging the nasal passages. Asthma treatment has been shown to greatly improve health related quality of life (HRQoL) and reduce the burden of asthma optimal. There was a statistical improvement in most parameters of the self-administered quality of life questionnaires and in all parameters of the interviewer-administered questionnaires. A minimal clinical important difference of 0.5 point per item was previously suggested.[17] Therefore, the clinical significance of this magnitude of improvement is questionable. Several studies concluded that halotherapy was beneficial; however, most of them included several respiratory diseases and were case controls studies. Improvement of FEV_1 and increased oxygen saturation following halotherapy were reported.[4,18]

A Cochrane review assessing speleotherapy for asthma concluded: "Due to the paucity of trials, the available evidence does not permit a reliable conclusion as to whether speleo-therapeutic interventions are effective for the treatment of chronic asthma. Randomized controlled trials with long-term follow-up are necessary." The mechanism by which speleotherapy may be beneficial is not clear. It may be due to air quality, underground, climate, irradiation, and hyperosmolar environment. Salt room chambers differ from speleotherapy and may mimic hypertonic saline inhalations. Hypertonic saline improved lung function in people with cystic fibrosis[19] and some studies suggested its use in bronchiolitis.[20] It probably works by reducing airway mucus gel. It may also osmotically increase the water content of the airway mucus, enhancing mucociliary clearance. Hypertonic saline can evoke cough and may also separate DNA from mucin, thereby reducing its viscosity. Thus, it may increase expectorated sputum.[21,22] Some studies suggest anti-inflammatory properties to hypertonic saline. A decrease in IL-8 was reported in CF patients.[23] Incubation of pulmonary epithelial cells with hypertonic saline inhibited both TNFα and IL-1β stimulated nuclear localization of interferon response factor 1 (IRF-1).[24]

Our study strength is its design. Yet, there are several limitations to our study; the main limitation is the small sample size. Both types I and II errors can occur in a small sample size. Additionally, the salt aerosol concentration was not measured, neither in the salt room with halogenerator nor in the room without halogenerator. We considered a salt room without salt halogenerator as a control room. If sitting in a salt room has an ameliorating effect, it may prevent a larger difference between the groups. However, most of the parameters remained unchanged in the control group, supporting the concept that a salt room without halogenerator can be considered as control. We assessed BHR by MCT, which causes a non-specific irritation, and not adenosine. We recruited mild asthmatic patients with relatively little room for improvement to allow ethically unproven treatment without denying indicated care. The conclusions, therefore, cannot be extended to more severe asthmatic children or children receiving anti-inflammatory treatment.

In conclusion, this study demonstrated that salt room therapy with halogenerator might exert a positive effect on non-specific airways reactivity and quality of life parameters. This effect was not associated with improvement in pulmonary function tests or FeNO, both considered as measures of asthma control. It is unknown if the positive reduction in BHR lasts beyond the treatment period and whether it may result in a lower exacerbation rate. Hence, at this point, recommendations for inclusion of halotherapy as a therapy for asthma cannot be made. Further studies are needed, including a larger sample size, more severe asthmatics as additive therapy and with long-term follow-up.

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