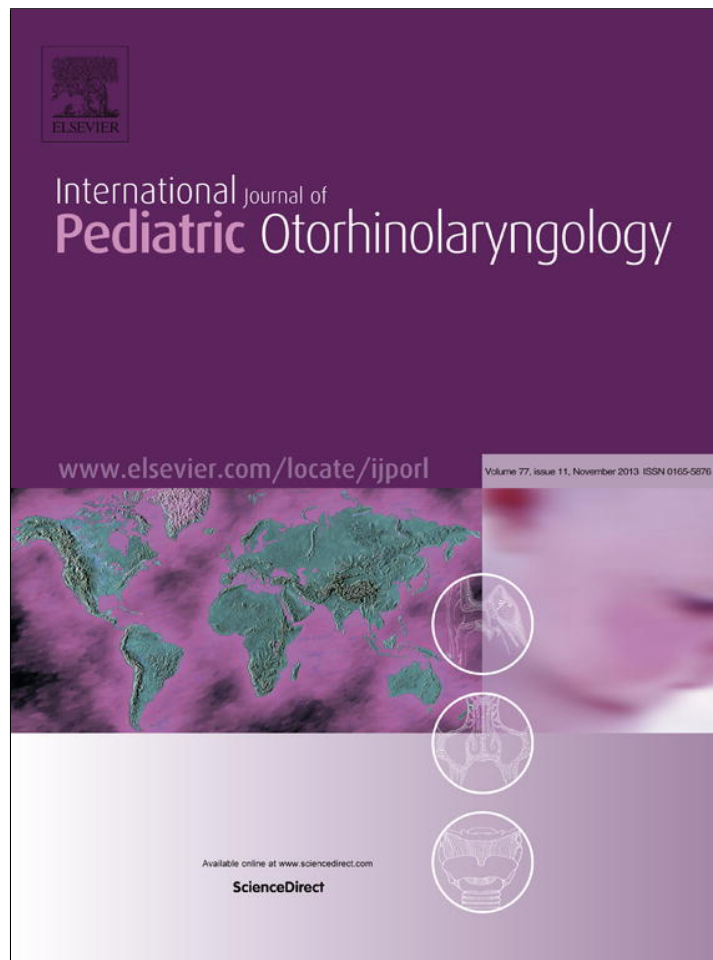


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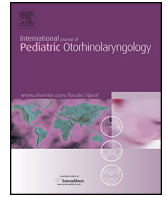
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Double-blind placebo-controlled randomized clinical trial on the efficacy of Aerosal[®] in the treatment of sub-obstructive adenotonsillar hypertrophy and related diseases^{☆,☆☆}



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ABSTRACT

Background: Adenotonsillar hypertrophy (ATH) is a frequent cause of upper airways obstructive syndromes associated to middle ear and paranasal sinuses disorders, swallowing and voice disorders, sleep quality disorders, and occasionally facial dysmorphisms. ATH treatment is essentially based on a number of medical–surgical aids including nasal irrigation with topical antibiotics and corticosteroids and/or treatment with systemic corticosteroids, immunoregulators, thermal treatments, adenotonsillectomy, etc.

Objectives: The aim of the present study is to assess the efficacy of Aerosal[®] halotherapy in the treatment of sub-obstructive adenotonsillar disease and correlated conditions compared to placebo treatment.

Methods: A total of 45 patients with sub-obstructive adenotonsillar hypertrophy were randomized to receive either Aerosal[®] halotherapy or placebo for 10 treatment sessions. The main outcome was a reduction greater than or equal to 25% from the baseline of the degree of adenoid and/or tonsillar hypertrophy.

Results: In the intention-to-treat analysis, a reduction of the degree of adenoid and/or tonsillar hypertrophy $\geq 25\%$ from baseline after 10 therapy sessions was found in 44.4% of the patients in the halotherapy arm and in 22.2% of the patients in the placebo arm ($P = 0.204$). Among the secondary outcomes, the reduction of hearing loss after 10 treatment sessions in the halotherapy arm was higher than the placebo arm ($P = 0.018$) as well as the time-dependent analysis showed significantly improved peak pressure in the Aerosal[®] group ($P = 0.038$). No side effects were reported during the trial. In addition, the therapy was well accepted by the young patients who considered it as a time for play rather than a therapy.

Conclusions: Aerosal[®] halotherapy can be considered a viable adjunct, albeit not a replacement, to conventional medical treatment of sub-obstructive adenotonsillar syndrome and related conditions. Further research is however needed to improve ATH treatment.

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1. Introduction

Symptomatic adenotonsillar hypertrophy (ATH) is a frequent cause of obstructive syndromes ascribable to mechanic obstruction in the oropharynx and resulting upper aerodigestive tract encumbrance [1]. The syndrome, which usually affects children aged 3–10 years, is characterized by middle ear, nasal passages, paranasal sinus symptoms, voice and swallowing disorders, poor sleep quality, and occasionally facial dysmorphisms and dental malocclusion [2–7].

ATH has a typical onset after the third year of life with symptoms progressively worsening with a peak age incidence between 4 and 8 years [8].

The management of this condition has changed dramatically over the last few years thanks to technological advances in diagnostic criteria specificity that once used to rely almost exclusively on rather empirical and vague clinical parameters [9,10]. As a result, it has been possible to define a more accurate nosologic picture of ATH which has allowed for a more targeted therapeutic strategy essentially based on the use of several therapeutic aids (topical antibiotics and corticosteroids to clear nasal passages and/or systemic corticosteroids, etc.) [11–19]. In this connection, in the past few years several investigators have studied the beneficial effects of salt (halotherapy from the Greek word for salt, *halos*) on a number of respiratory system conditions (rhinosinusitis, allergic rhinitis, otitis, bronchitis, and asthma) [20–23] as well as on some dermatological pathologies (atopic dermatitis and psoriasis) [24–26]. Halotherapy is based on a non pharmacological approach as it relies on the release of micronized medical sodium chloride into an indoor climate-controlled environment. The release is meant to recreate the conditions occurring in nature in salt mines and caves. Occasionally a small amount of micronized iodine is added to mimic the experience of being on a real naturally occurring seashore. Salt therapy has been practised in old salt mines of Central and Eastern Europe for centuries where it is still common being considered a full-fledged medical treatment.

The aim of the present study was to assess the efficacy of Aerosal[®] in the treatment of sub-obstructive adenotonsillar hypertrophy and correlated disease versus placebo treatment.

2. Materials and methods

2.1. Patients

Patients were recruited from the Department of Otolaryngology (ENT) of Bari University General Hospital after approval had been obtained by the institutional ethics committee. Inclusion criteria were as follows: age range: 4–12 years; genders: both; pathology: sub-obstructive adenoid hypertrophy lasting from at least six months and associated with sleep-disordered breathing (respiratory pauses or sleep apnea) and/or recurrent serous otitis media; suspension for over 3 months from the start of the study of any immunosuppressive treatments (cyclosporin and systemic steroids). Exclusion criteria: patients with acute bronchopulmonary disease, tuberculosis, severe hypertension, hyperthyroidism, cancer (chemotherapy), intoxication, heart failure, bronchial asthma or iodine allergy. Patients were still allowed to use topical therapy with nasal washings and topical steroids.

2.2. Technical specifications of salt room “Aerosal[®]”

2.2.1. Salt room

Both walls and ceiling of the multilayer sea wood salt room (2.30 mt. × 2.90 mt. × 2.20 mt.) are completely covered with ESCO (European Salt Company) type certified-origin iodized rock salt. The floor, which is also made of multilayer sea wood, is covered with about 500 kg of RESIMAX type certified-origin rock salt (Figs. 1 and 2).

The room environment is not contaminated with pathogenic microorganisms (as certified by SAS 90[®] measurements). Patients can settle into comfortable chairs inside the room where the dry salt aerosol is blown through a PVC pipe (described below). A centrifugal extractor fan (air flow rate 90 m³/h), placed on the side opposite to the PVC pipe ensures a number of complete changes of air in full compliance with requirements in terms of CO₂ ppm values, i.e. <750 ppm. Also temperature and humidity are kept at constant values ranging between 20 °C and 24 °C and 44% and 60%, respectively (TESTO 435-4[®] Digital Multimetric measurements).

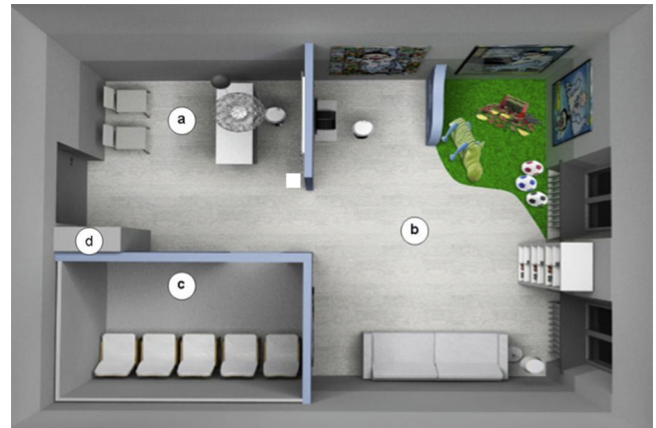


Fig. 1. “Salt Clinic”. 3D design: reception/welcome area (a); waiting room with children's recreation area (b); “Aerosal[®]” halotherapy room (c). ENT Care Unit (d). Cabinet containing the Dry Salt Aerosol Generator – University General Hospital – Bari (Italy).

2.2.2. Dry salt aerosol generator

The dry salt aerosol generator is encased in a cabinet placed outside of, albeit contiguous to, the salt room (Fig. 1d). A standard amount of NaCl (salt sachet) is fed into the dry salt aerosol generator to be blown into the salt room in the form of aerosol through a PVC (polyvinyl chloride) connector. The size of NaCl, micronized particles ranges from 0.23 to 20 μm (data collected by portable laser aerosol spectrometer Model 1.109 with GRIMM[®] technology). Particle density ranges from 20 to 35 μg/m³ and is kept constant over time thanks to an electronic system.

2.2.3. Salt sachet: salt features

The salt sachet contains 30 g of NaCl, 20 g of micronized RG (Reagent Grade) salt (according to Ph Eur Current Edition), and 10 g of non micronized ESCO iodized feed salt to prevent aggregation and keep an appropriate level of iodine exposure.

2.3. Clinical and instrumental evaluation

After collection of medical history, all the patients underwent clinical and instrumental exams as follows: ENT visit with inspection of the oropharyngeal tract and tonsillar hypertrophy staging (0°–4°) [27], flexible fibroscope nasal endoscopy (ENT 2000



Fig. 2. “Aerosal[®]” Halotherapy Salt Room where children are always highly compliant as they consider treatment sessions as opportunities for play and recreation. ENT Care Unit–University General Hospital – Bari (Italy).

flexible Ø 3.4 mm fibroscope – Vision Sciences[®], USA) to assess the degree of adenoidal hypertrophy [10]. Pure tone audiometry was performed in a sound-proofed cabin using pure tones (250 ms duration, 25 ms rise/fall time, 50% duty cycle) at octave frequencies from 125 Hz to 8000 Hz with a maximum intensity of 120 dB SPL with an Amplaid 309 clinical audiometer (Amplaid, Milan, Italy). Tympanometric measurements were performed using a 220 Hz probe tone with an Amplaid 770 clinical tympanometer (Amplaid, Milan, Italy). Air conduction pure tone average was obtained by the mean of thresholds at 0.5, 1, 2 and 4 kHz. Tympanograms were classified according to Jerger in types A, B and C [28]. Nasal cytology was performed by anterior rhinoscopy, using a nasal speculum and good lighting. Scrapings of the nasal mucosa were collected from the middle portion of the inferior turbinate, using a Rhino-Probe[®] [29]. Samples were placed on a glass slide, fixed by air drying and then stained with the May-Grunwald Giemsa (MGG) method (Carlo Erba[®], Milan, Italy) [30]. Cell counts, bacterial and fungal analysis were carried out by a semi-quantitative grading, as proposed by Meltzer and Jalowayski [31]. The semiquantitative evaluation of the biofilms [32] was performed by counting the number of infectious spots (ISs) in 50 microscopic fields, always at a 1000× magnification (oil immersion). Sleep evaluation was carried out overnight by means of wrist-worn pulse oximeters Wrist O₂[™] Model 3150. The parameters studied were: basal SpO₂%; event data index (adjusted index, 1 h⁻¹) and time (%) with SpO₂ value below 95%. It was decided to use pulse oximetry [33] instead of “gold standard” polysomnography [34] to study patients' sleep patterns as the former makes overnight studies easier for patients at home (the protocol envisaged three such studies in three months, two of them with only a 15-day interval). In addition, important guidelines [35,36] do indicate pulse oximetry as a method with a high positive predictive value of OSASs (97%) [37].

2.4. Study design

After having given their written informed consent all the eligible patients were randomized on a 3:2 basis to receive either Aerosal[®] or placebo. Central stratified blocked randomization using telephone was adopted with patients, investigators and outcomes assessor being all blinded to randomization rules. Aerosal[®] treatment consisted of 10 daily sessions (5 sessions for week) of micronized iodized salt (sodium chloride) – with the addition of iodine – inhalation in a chamber reproducing the microclimate of a natural salt cave. Each daily session lasted 30 min. Treatment with placebo comparator was performed in the same way as halotherapy but with no salt release in the room. All patients underwent a complete clinical evaluation at baseline, at the end of therapy period (10 sessions) and 3 months after the end of treatment (follow-up).

2.5. Outcome measures

The primary outcome measure, evaluated both after 10 sessions of therapy and at the 3-month follow-up, was an adenoid and/or tonsillar hypertrophy reduction $\geq 25\%$ from baseline as assessed by the physician on a standardized four-point rating scale. Secondary outcome measures included instrumental assessments: any reductions in terms of adenoid and/or tonsillar hypertrophy degree; any reductions of hearing loss ≥ 10 dB of the 4-frequency (0.5, 1, 2 and 4 kHz) pure tone average, as well as any other significant gain; any improvements in of tympanometric values, i.e. transition from type B curve to type C/A curve or from type C curve to type A curve for both sides; any change in tympanogram peak pressure (daPa); any changes in pulse-oximetric values (increase in SpO₂% mean levels, reduction of the event data index

(adjusted index, 1 h⁻¹), reduction of sleep time percentage with SpO₂ levels <95%; any reductions of the main inflammatory immune cells (neutrophils, eosinophils, and mast cells) as assessed by nasal cytology. The number of side effects reported either during treatment period or after the end of treatment, if suspected to be related with this latter, was also included in secondary outcome measures.

2.6. Statistical analysis

Data were presented as medians with ranges and/or inter-quartile ranges (IQRs), or numbers with percentages. Baseline variables and changes in outcomes were compared between groups by using the Mann–Whitney *U* test for continuous data and Fisher's exact test for categorical ones. Overall time-dependent variations in primary and secondary outcomes were evaluated by Friedman's test for repeated measures with Page's test for trend in time variations. An intention-to-treat approach was adopted in primary analyses. This approach considered patients withdrawn prematurely from the study as treatment failures in the two study arms. Intention-to-treat analysis was then complemented by per-protocol analyses which considered only those patients who had completed the study period. In the study design phase it had been calculated that a total of 64 patients would be needed for the study to have a 40% success rate in terms of primary outcome in the halotherapy group as against 10% in the placebo group ($\alpha = 0.05$, $\beta = 0.20$). Statistical analysis was carried out by using MATLAB software (MathWorks, Natick, MA, USA). Two-sided *P*-values <0.05 were considered to indicate statistical significance in all tests.

3. Results

Between February 2012 and March 2012, 49 patients were screened, 45 of whom (24 boys and 21 girls, average age 6 years) underwent randomization. The reason for exclusion was age outside the study inclusion criteria age range ($n = 4$). Recruitment halted prematurely due to technical and legal issues related to the certification of the device. The baseline characteristics of randomized patients in the two arms of the study are given in Table 1. One patient, randomized to the placebo group, withdrew after the first week of treatment for an episode of acute tonsillitis requiring antibiotic treatment, and one patient, randomized to the Aerosal[®] arm, withdrew during the follow-up period for exacerbation of upper airways symptoms. Both arms were matched in baseline characteristics (data not shown).

3.1. Effectiveness

Fig. 3 shows the distribution of variations of measurements from baseline in both arms after 10 treatment sessions in terms of (i) reduction of the degree of adenoid and/or tonsillar hypertrophy; (ii) reduction of hearing loss and (iii) tympanometry improvement. All outcome measures and their departure from baseline at the end of treatment sessions and at the 3-month follow up are reported in Table 2. Assuming intention-to-treat analysis as a reference, a reduction of the degree of adenoid and/or tonsillar hypertrophy $\geq 25\%$ from baseline after 10 therapy sessions was found in 44.4% of the patients in the halotherapy arm and in 22.2% of the patients in the placebo arm ($P = 0.204$). These results increased to 59.3% and 38.9%, respectively at the 3-month follow up ($P = 0.231$). Other substantial changes in adenoid or tonsillar hypertrophy were not found to have a statistical significance at any other point in time.

Among secondary outcomes hearing loss reduction was found to be significant ($P = 0.018$) after 10 treatment sessions in the halotherapy arm compared to the placebo arm, even though the

Table 1
Baseline characteristics of randomized patients.

	Aerosal (N=27)			Placebo (N=18)		
	N (%)	Median (IQR)	Range	N (%)	Median (IQR)	Range
Gender (male/female)	14 (51.9)			10 (55.6)		
Age		6 (4)	4–12		4.5 (2)	4–10
Weight (kg)		25 (13.5)	15–56		20 (5.5)	14–41
Height (cm)		120 (24.2)	97–160		110 (10)	95–131
BMI (kg/m ²)		17.4 (2.3)	14.3–25.5		16.9 (3.5)	11.6–23.9
ATH age at onset (years)		3 (2.5)	0–7		2 (1)	1–6
ATH duration (years)		3 (5.2)	1–9		2 (1)	1–5
ATH familiarity	13 (48.2)			6 (33.3)		
Previous topical treatments	19 (70.4)			13 (72.2)		
Previous systemic treatments	21 (77.8)			10 (55.6)		
Previous ENT pathologies	22 (81.5)			14 (77.8)		
Current topical treatments	5 (18.5)			4 (22.2)		
Adenoid hypertrophy degree		3 (0)	3–4		3 (0)	2–4
Tonsillar hypertrophy degree		3 (0.8)	1–4		3 (1)	1–4
Nasal cytology						
Neutrophils (any)	17 (63.0)			11 (61.1)		
Eosinophils (any)	9 (33.3)			2 (11.1)		
Mast cells (any)	3 (11.1)			1 (5.6)		
Audiometry (dB) ^a		17.5 (19.4)	10–40		15 (25)	10–45
Tympanometry (right)						
Type A curve	10 (37.0)			4 (22.2)		
Type B curve	12 (44.4)			7 (38.9)		
Type C curve	5 (18.5)			7 (38.9)		
Tympanometry (left)						
Type A curve	6 (22.2)			5 (27.8)		
Type B curve	18 (66.7)			8 (44.4)		
Type C curve	3 (11.1)			5 (27.8)		
Tympanometric peak, right (daPa)		–168 (126)	0–302		–214 (123.8)	0–296
Tympanometric peak, left (daPa)		–223.5 (124)	0–304		–240 (133.5)	28–300
Pulse-oximetry indexes						
Mean SpO ₂ % levels		96 (1.6)	91.4–97.6		96.1 (2.2)	89.3–97.5
Apnea events (1 h ⁻¹)		1.2 (4.1)	0–24.5		1 (1.4)	0–9
Sleep time % with SpO ₂ <95%		11.4 (25.7)	0.1–95.9		8.5 (41.5)	0–87.6

ATH, adenotonsillar hypertrophy; ENT, otolaryngology; IQR, interquartile range; range = Min – Max. There were no significant differences in baseline characteristics between the two arms of the study.

^a Average audiometry (left/right) evaluated at the frequencies of the tone range (0.5, 1, 2, 4 kHz).

difference between the two arms was not statistically significant at follow up ($P = 0.107$). The overall time-dependent analysis of variations showed a significant difference between the two arms for hearing loss reduction with a significant decreasing trend

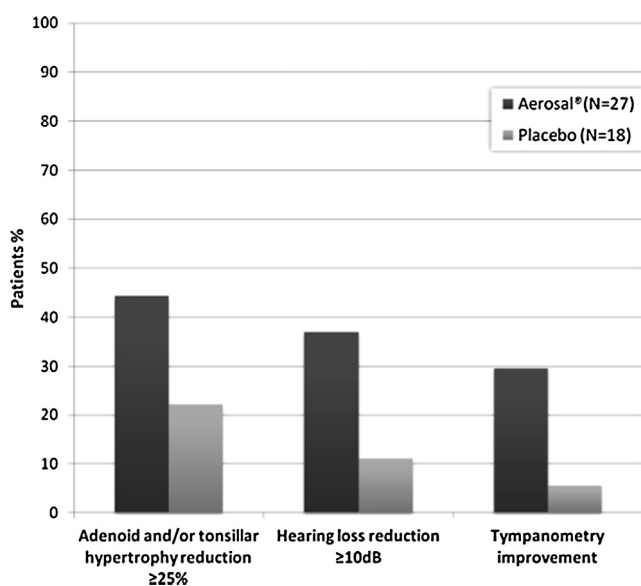


Fig. 3. Distribution of study arms after 10 treatment sessions from baseline according to reduction of adenoid and/or tonsillar hypertrophy degree, hearing loss reduction and tympanometry improvement.

($P = 0.010$) in the treatment arm, while no significant trend was observed in the placebo arm ($P = 0.165$).

The analysis of the tympanograms showed that after 10 treatments tympanogram type improved in 29.6% of the patients in the Aerosal[®] arm compared to 5.6% of patients in the placebo arm ($P = 0.064$). No difference was however observed between the two arms at the 3-month follow up. Also in this case the time-dependent analysis showed significantly improved tympanogram in the Aerosal[®] group compared to the placebo group on both sides ($P = 0.002$). A significant trend was observed for both sides in the treatment arm ($P = 0.005$ for the right side and $P < 0.001$ for the left side), while in the placebo arm a significant improvement was observed only on the left side ($P = 0.015$). The analysis of the peak compliance showed that even if at T_1 and T_2 there were no significant differences between the two groups in terms of peak changes, the time-dependent analysis showed significantly improved peak pressure in the Aerosal[®] group compared to the placebo group on both sides ($P = 0.038$).

The other secondary outcomes did not exhibit major differences between the two arms.

In more detail, as far as nasal cytology is concerned, 37.0% of patients in the Aerosal[®] arm and 22.2% of patients in the placebo group exhibited a reduction $\geq 50\%$ of the principal inflammatory immune cells after 10 treatment sessions ($P = 0.343$). These proportions were found to be 37.0% and 33.3%, respectively at follow up evaluation ($P = 1$).

Regarding pulse oximetry values, baseline SpO₂ did not show any statistically significant variation after 10 sessions ($P = 0.880$), as was the case for the other two parameters under study, i.e.

Table 2
Intention-to-treat analysis of primary and secondary outcomes at T₁ (10 sessions of therapy) and T₂ (3 months from the end of treatment) compared to baseline.

	Aerosol (N=27)		Placebo (N=18)		P-value ^a
	N (%)	Median (IQR)	N (%)	Median (IQR)	
T₁					
Reduction of adenoid hypertrophy degree (%)		0 (25)	0 (0)		0.734
Reduction ≥25%	8 (29.6)		3 (16.7)		0.482
Reduction of tonsillar hypertrophy degree (%)		0 (31.2)	0 (0)		0.197
Reduction ≥25%	9 (33.3)		3 (16.7)		0.308
Reduction of adenoid and/or tonsillar hypertrophy degree ≥25%	12 (44.4)		4 (22.2)		0.204
Hearing loss reduction ^b (dB)		5 (13.8)	0 (10)		0.018
Reduction ≥10 dB	10 (37.0)		2 (11.1)		0.086
Tympanometry improvement ^c	8 (29.6)		1 (5.6)		0.064
Tympanometric peak pressure change (daPa)		-21.5 (79.5)	-1 (74)		0.141
Nasal cytology reduction ^d ≥50%	10 (37.0)		4 (22.2)		0.343
Increase of mean SpO ₂ % levels		-0.1 (1.9)	0.1 (2.8)		0.880
Reduction of apnea events (1 h ⁻¹)		-0.5 (4.9)	0 (1.4)		0.372
Reduction of sleep time % with SpO ₂ <95%		3.6 (14.6)	-2.5 (57.4)		0.424
T₂					
Reduction of adenoid hypertrophy degree (%)		0 (18.8)	0 (25)		0.967
Reduction ≥25%	7 (25.9)		6 (33.3)		0.739
Reduction of tonsillar hypertrophy degree (%)		0 (31.2)	0 (0)		0.070
Reduction ≥25%	11 (40.7)		3 (16.7)		0.111
Reduction of adenoid and/or tonsillar hypertrophy degree ≥25%	16 (59.3)		7 (38.9)		0.231
Hearing loss reduction ^b (dB)		2.5 (14.4)	0 (10)		0.107
Reduction ≥10 dB	10 (37.0)		4 (22.2)		0.343
Tympanometry improvement ^c	9 (33.3)		3 (16.7)		0.308
Tympanometric peak pressure change (daPa)		-60.5 (104.4)	-44 (78.5)		0.509
Nasal cytology reduction ^d ≥50%	10 (37.0)		6 (33.3)		1
Increase of mean SpO ₂ % levels		0.2 (2.2)	0.2 (2)		0.772
Reduction of apnea events (1 h ⁻¹)		0.2 (2.8)	-0.9 (2.1)		0.102
Reduction of sleep time % with SpO ₂ <95%		0.4 (28.5)	0.3 (22.2)		0.917

IQR, interquartile range.

^a Mann–Whitney *U*-test for continuous variables, Fisher's exact test for categorical variables.

^b Reduction of average audiometry (left/right) evaluated at the frequencies of the tone range (0.5, 1, 2, 4 kHz).

^c Improvement was defined as defined as the passage from type B curve to type C/A curve or from type C curve to type A curve for both ears sides.

^d Any reduction of principal inflammatory immune cells (neutrophils, eosinophils, and mast cells).

reduction of the event data index ($P=0.372$), and reduction of sleep time with SpO₂ <95% ($P=0.424$). Pulse oximetry values remained mostly unchanged at follow up.

The results of the per-protocol analysis did confirm the main findings and were generally overlapping intention-to-treat outcomes (data not shown).

4. Discussion

The growing prevalence of conditions (both allergic and infectious) affecting the upper airways has stimulated a whole series of studies on topical treatments in a view to reducing the side effects of systemic treatments and improving clinical response in terms of improvement of nasal symptoms [38–40].

The latest guidelines issued by EPOS 2012 [41] on obstructive and infectious nasal sinus disease include among therapeutic aids (antibiotics, topical steroids, and topical decongestants) also nasal saline irrigation, thus emphasizing the crucial role of this treatment in reducing nasal congestion and mucopurulent discharge by a washing process that restores mucociliary clearance and prevents both locoregional (otitis, rhinosinusitis) and distant inflammation (rhinobronchial syndrome, bronchitis, pneumonia, asthma, etc.) [42–44].

In addition, in the last few years some literature studies [20–26] have reported a new therapeutic-preventive role for sodium chloride in what has come to be called “halotherapy” and in the applications of this latter in the different branches of medicine, in particular respiratory and dermatological disease. As a matter of fact, for hundreds of years salt has been recognized as an agent to treat respiratory and skin conditions. The history of using salt caves for healing (speleotherapy from Greek *speleos* = cave and therapy)

different ailments by assimilating dust-like salt particles goes back to ancient times. These caves used for therapeutic purposes are still in use in many Central and Eastern European countries including Austria (Solzbad-Salzetnan), Romania (Sieved), Poland (Wieliczka, one of the UNESCO World Heritage Sites), Azerbaijan (Nakhichevan), Kirgizia (Chon-Tous), Russia (Berezniki-Pern), and Ukraine (Solotvino-Carpathians e Artiomovsk-Donietsk).

The possibility of recreating the microclimate (Table 3) of these caves in a room has given a new impulse to studies and research efforts on the potential therapeutic effects of this treatment.

As far as the present study is concerned, the first finding has been the absence of adverse effects. None of the children enrolled in the study exhibited episodes of respiratory distress (dyspnea, bronchial hyperactivity, asthma), skin itch or eyes disorders, both during treatment and in the hours immediately after treatment. In addition, a high compliance to treatment has been observed as children did not consider their HT sessions as a therapy, but rather as a time for play or recreation as they spent their 30-min sessions playing, watching TV (cartoons, wildlife shows, etc.) (Fig. 2). Only two children withdrew from the study; one of them (in the placebo arm) withdrew during the first week of halotherapy for an episode

Table 3
Salt room microclimate features.

Size of iodized NaCl particles released	0.23–20 μm
Particles density	35–50 μg/m ³
Air exchange	90 m ³ /h
CO ₂ ppm	<750
Temperature	20–24 °C
Humidity	44–60%

of acute tonsillitis with high fever, the other dropped out in the follow-up period for increased adenotonsillar hypertrophy associated with sleep respiratory disorders with an indication for adenotonsillectomy. Being specific to the natural course of the conditions in question, these episodes have not been considered as adverse events connected to the halotherapeutic treatment.

However the most interesting aspects emerging from the present study have been those related to the assessment of the real impact of halotherapy on both the lymphatic component (adenotonsillar component) and co-morbidities, namely ear conditions and sleep disorders. Actually, the numerous studies conducted so far on halotherapy have mainly been focused on lower airways conditions (cystic fibrosis, bronchitis, and asthma [21–23]).

Our study has highlighted a $\geq 25\%$ reduction of the adenotonsillar tissue in 44.4% of the patients treated versus 22.2% of the placebo controls. In our view, far from being statistically significant ($P = 0.204$), this finding has a clinical value that deserves further study. This pattern has also been confirmed by the pulse-oximetric data that, far from being statistically significant, have shown a decreased event data index (adjusted index) as well as a reduction of the sleep time percentage with $SpO_2 < 95\%$. Based on our results it is possible to calculate that approximately 140 patients (70 in each arm) would be needed to show a significant reduction of the adenotonsillar tissue as expressed in the primary outcome. It is therefore unlikely that the loss of power due to the reduced number of patients enrolled in the study (45) compared to the planned number (64) had a significant impact on our findings. The reduction of some clinical and endoscopic parameters also in the control group should however be justified by the fact that the very young patients actually spent their time in a “salted” environment where their same manipulation of salt released microparticles of sodium chloride available for inhalation.

Among secondary end-points, end-of-treatment improvement of hearing loss has been found to be statistically significant in the halotherapy group ($P = 0.018$) compared to the control group. The statistical analysis has demonstrated a significant improvement of both tympanogram and hearing loss in the Aerosal[®] group.

The treatment of otitis media with effusion (OME) is still controversial today. While this condition has a high likelihood of a spontaneous recovery [45], so far no medical therapy has been shown to be effective to treat OME, as indicated by recent reviews [46–49]. The presence of a control group in our study does rule out the possibility that the improvements observed are linked only to a spontaneous recovery from the disease. Even though the effectiveness of sodium chloride in OME treatment has never been reported in literature studies, the potential mechanisms of action could be ascribed to decongestion of nasal passages and tubaric orifice respiratory mucosa as well as to a restored mucociliary clearance that would favor middle ear aeration-draining mechanisms. This assumption is substantiated by literature studies that report the efficacy of those treatments targeted to improve middle ear ventilation. Perera et al. reported some evidence that autoinflation devices may be of benefit in the short-term in treating children with otitis media with effusion [50]. Similar results were reported in a group of children affected by OME treated with swallowing and auto-inflation exercises, including Valsalva maneuver [51]. Finally even if the improvement of hearing threshold was on average of only 5 dB, it is important to remember that the pre-treatment threshold was on average between 15 and 17.5 dB, therefore a 5 dB change together with a change in tympanogram is clinically relevant. A longer treatment could however further improve the hearing thresholds.

No statistically significant difference has been found in terms of sleep quality and nasal immunophlogosis parameters. Recent work on bronchial immunophlogosis confirms these findings [52].

5. Conclusions

Halotherapy accounts for a relatively new, completely natural therapeutic remedy which does not call for any pharmacological administration and is based on the healing capacities of natural salt micronized and released into an indoor environment by means of specific techniques. Halotherapy administered by Aerosal[®] system has been shown to have a statistically significant effect on OME. Aerosal[®] halotherapy has also been found to be partially effective in reducing adenotonsillar hypertrophy. The beneficial effects of the treatment in question have been shown for some “time-dependent” parameters, therefore additional studies should be conducted in a view to defining treatment modalities likely to result in a better clinical response. New double-blind, placebo-controlled, randomized clinical studies should also be performed on more complex conditions including asthma, cystic fibrosis, chronic pulmonary disease and dermatological conditions.

In addition to being a safe treatment, the Aerosal[®] Halotherapy system has been well accepted and tolerated by our young patients who experienced their halotherapeutic sessions as a time for play and recreation and not as a real medical treatment. Therefore Aerosal[®] Halotherapy might constitute a valuable adjunct (and not a replacement) to current orthodox medical treatment of adenotonsillar disease and correlated conditions.

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Conflict of interest

None declared.

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