רות
בית חולים רות רפפורט לילדים
רמב"ם-הקריה הרפואית לבריאות האדם

True or Mist ?

Nir Kugelman
Ronen Bar-Yoseph
Lea Bentur
Pediatric Pulmonary Institute, February 2015

Asthma treatment

- Requires proper technique
- High failure rate (poor technique, poor compliance)
- Fear of adverse events
- Unlike asthma symptoms, asthma progression is insensitive to inhaled corticosteroids

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Alternative treatments as complements or replacements to conventional treatments

Halotherapy

- Salt therapy consists of sitting in a salt cave in eastern Europe

Salt room

- Salt room coated with salt crystals and pumped full of salt-laden air
- The experience is designed to approximate that in the naturally occurring salt caves in Eastern Europe
- Halotherapy centers are popping up increasingly in the U.S., Europe and Canada
- Less effective than real cave

Salt walls and floor + halogenerator

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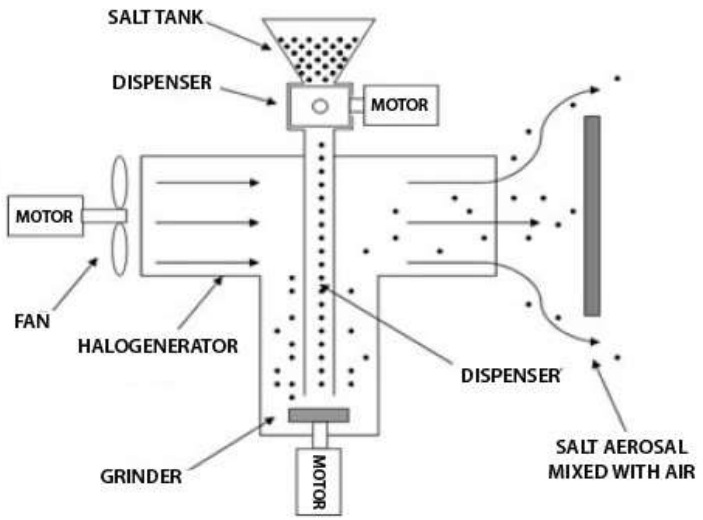

- Halogenerator → produces dry salt aerosol by mechanically crushing rock salt grains to the size of 1-5 micrometers

Salt room chambers

Very popular as an alternative treatment for asthma

Paucity of scientific research to support their effectiveness

Aim

To evaluate the effect of halotherapy on BHR, inflammatory process in the airways and quality of life in children.

Methods

- The study was approved by Ethic Committees (0059-12)
- Setting: Out patients clinic, Pediatric Pulmonary Institute
- Design: Randomized, double-blind placebo-controlled study

Salt room- passive

Active salt room

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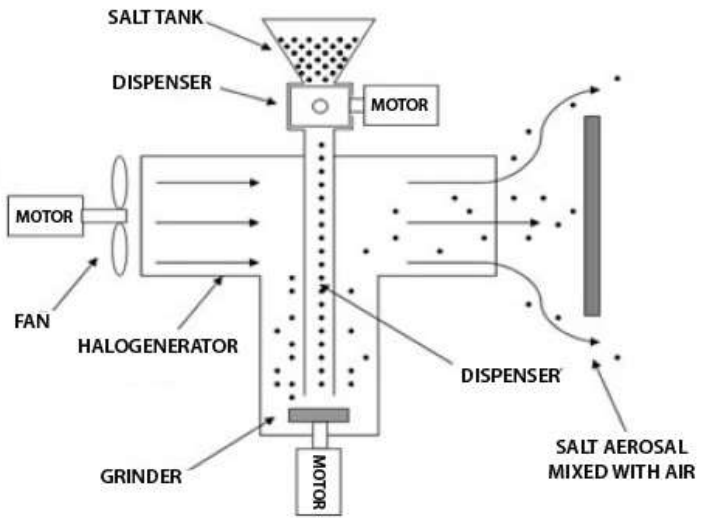

Inclusion criteria

- Children aged 5-13 years
- Mild asthma according to GINA
- Not receiving constant anti-inflammatory therapy in the month that preceded the study
- Capability of performing spirometry, FeNO

Exclusion criteria

- FEV_1<70%
- Presence of other respiratory diseases
- Emergency room visit or hospital admission in the three months prior to the study
- Usage of PO Steroids in the month that preceded the study

Outcome parameters

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Primary end point:

- Metacholine challenge test (PC_{20} and stage number)

Secondary end points:

- Spirometry
- FeNO – Fractional Exhaled NO
- Pediatric Asthma Quality of Life Questionnaire (PAQLQ)

Visit 1

- ✓ Written parental consent
- ✓ PAQLQ questionnaires
- ✓ Asthma history questionnaire
- ✓ Spirometry
- ✓ Metacholine challenge test
- ✓ FeNO
- ✓ Proceed to 7 weeks (14 cessions of 45 minutes) in a salt room (passive / active)

Visit 2

After 7 weeks → re-evaluation

- ✓ Spirometry
- ✓ MCT
- ✓ FeNO
- ✓ Quality of life questionnaires

Sample size

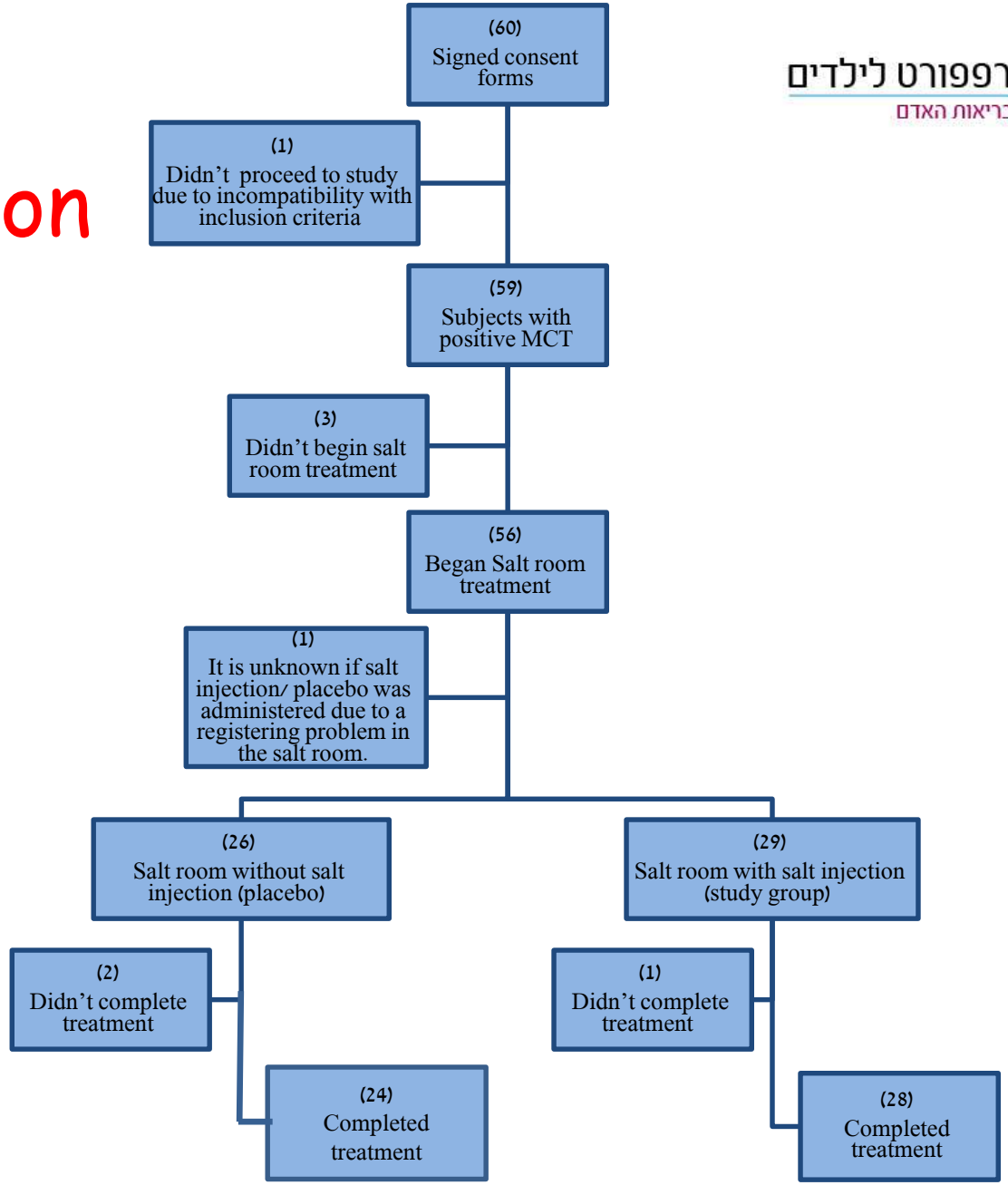
- Sample size was calculated according to PC_{20} using Win Episcope 2.0

- A sample size of 36 patients is necessary to detect an increase in MCT from 4±1 to 5±1 mg/ml, with a power of 80% and confidence level of 95.

Statistics

- Paired and unpaired t-test
- Fisher exact test ,Pearson chi square test
- Normal distribution by Kolmogorov Smirnov
- Mean ± SD, median and 25-75%ile
- $p<0.05$ was considered as statistical significance

Study population



Results

- Population characteristics
- Asthma history
- Baseline measurements
- First visit quality of life questionnaires

No statistical difference between the groups

Demographics

Parameter	Placebo	Salt injection	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

Asthma history

Parameter	Placebo N=27	Salt injection N=30	p-Value
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 induced Exacerbation	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

Baseline measurements

Parameter	Placebo- first visit N=27	Salt injection- first visit N= 30	p- Value
PC_{20} mean (mg/mL)	2.4±3.2	2.2±3.04	NS
PC_{20} median (mg/mL) (25%-75% percentile)	1.5 (0.13-2.74)	0.96 (0.11-3.19)	NS
Stage of PC_{20} mean	3.9±1.6	3.6±1.7	NS
Stage of PC_{20} median (25%-75% percentile)	4 (2-5)	4 (2-5)	NS
FEV_1 (% predicted)	86.4±10.3	91.7±12.5	NS
FEV_1/FVC (% predicted)	102.1±9.3	101.4±8.4	NS
FEF_{25-75} (% predicted)	80.5±19.7	84.0±18.7	NS
FeNO mean (ppb)	23.8±20.54	31.3±33.2	NS
FeNO median (range) (ppb)	17.4 (76)	18.6 (200)	NS

First visit quality of life self-administered questionnaire

Parameter	Placebo – first visit N=27	Salt injection – first visit N=26	P- value
Symptoms average	6.42±0.74	6.26±0.79	NS
Activity limitation average	5.86±1.39	5.75±1.19	NS
Emotional function average	6.53±0.884	6.43±0.74	NS
Weighted average	6.34±0.83	6.21±0..74	NS

First visit quality of life interviewer-administered questionnaire

Parameter	Placebo-first visit N=24	Salt injection-first visit N=28	p- Value
Symptoms average	6.5±0.66	6.35±0.71	NS
Activity limitation average	6.28±0.99	6.12±0.9	NS
Emotional function average	6.64±0.72	6.52±0.66	NS
Weighted average	6.5±0.7	6.36±0.68	NS

Results after intervention…

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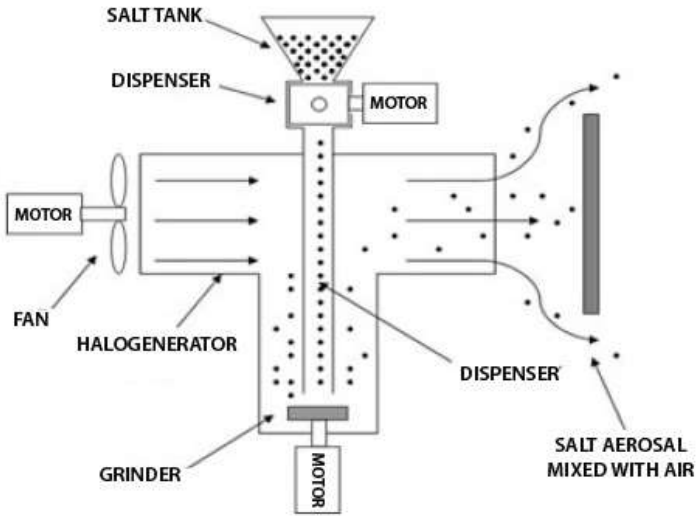

Variables before and after treatment

	Placebo N=24		Salt injection N=28		
Parameter	Before treatment	After treatment	Before treatment	After treatment	p-Value
PC_{20} mean (mg/mL)	2.61±3.35	2.24±2.75	2.23±3.14	6.41±7.36	[1]NS [2]0.044
PC_{20} median (ppb), (25%-75% percentile)	1.64 (0.16-2.87)	0.89 (0.10-3.61)	0.96 (0.11-3.43)	2.62 (0.32-16)	[1]NS [2]0.044
Stage of PC_{20} mean	4.1±1.6	3.9±1.8	3.7±1.6	4.7±2.1	[1]NS [2]0.04
FeNO mean (ppb)	22.01±18.39	28.97±31.0	35.49±37.79	38.16±35.05	[1]NS [2]NS
FeNO median (ppb) (25%-75% percentile)	16.7 (6.3-36.1)	20.6 (11.7-36.8)	20.55 (9.1-38.8)	22.05 (12.4-59.1)	[1]NS [2]NS

Variables before and after treatment

	Placebo N=24		Salt injection N=28		
Parameter	**Before treatment**	**After treatment**	**Before treatment**	**After treatment**	***p*-Value**
FEV_1 (% predicted)	86.4±9.5	81.8±12.3	91.2±12.7	86.1±11.9	[1]0.003 [2]0.003
FEV_1/FVC (% predicted)	102.2±9.4	98.3±9.8	101.2±8.6	99.4±8.4	[1]0.008 [2]NS
FEF_{25-75} (% predicted)	79.6±18.4	70.5±20.3	83.1±18.9	78.41±21.4	[1]0.007 [2]0.046

Self-administered questionnaire

	Placebo N=23		Salt injection N= 21	
Parameter	**Before treatment**	**After treatment**	**Before treatment**	**After treatment**
Symptoms average	6.47±0.16	6.27±0.98	6.32±0.84	6.78±0.32
	NS ←		P=0.016	
Activity limitation average	6±1.33	6.09±1.33	5.85±1.18	6.35±0.75
	NS ←		NS (P= 0.051)	
Emotional function average	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	

Interviewer-administered questionnaire

	Placebo N=23		Salt injection N= 28	
Parameter	**Before treatment**	**After treatment**	**Before treatment**	**After treatment**
Symptoms average	6.59±0.46	6.56±0.61	6.5±0.69	6.7±0.65
	NS ←		P=0.029	
Activity limitation average	6.58±0.53	6.68±0.51	6.21±0.86	6.49±0.8
	NS ←		P=0.017	
Emotional function average	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	

Results

- A statistical significance improvement in bronchial hyper- responsiveness (BHR) was demonstrated in the study group which remained unchanged in the placebo group- PC_{20} and Stage of PC_{20}.
- No change in FeNO levels following treatment in both groups.
- No improvement in spirometry following treatment in both groups.

Results

- Study group → statistical improvement in most parameters of the self-administered quality of life questionnaires + all parameters of the interviewer-administered questionnaires.

- Remained unchanged in the placebo group.

Literature

- Adults: The effect of salt chamber treatment on BHR in asthmatics
- Randomized, double-blind placebo-controlled study, age > 18
- 22/32 finished the study
- Halotherapy complementary to ICS .
- Treatment: 5 times/wk for 2 weeks.
- Halotherapy with salt injection → improvement in BHR.
- No change in spirometry

Allergy 2006;61(6):789

Non controlled studies

- A review of halotherapy for chronic obstructive pulmonary disease, Int J Chron Obstruct Pulmon Dis. 2014 Feb 21;9:239-46.
- Halotherapy for treatment of respiratory diseases. J Aerosol Med. 1995;8:221–232.
- Efficacy of Halotherapy for Improvement for Pulmonary Function Tests and Quality of Life of Non-Cystic Fibrosis Bronchiectatic Patients. Tanaffos. 2013;12:22–27

Possible Mechanism

- NEJM → Inhaled hypertonic saline improved lung function in people with cystic fibrosis.

- ERJ → found that inhaled aerosolized salt in smokers temporarily improved smoking-related symptoms such as coughing and mucus production.
- Hypertonic saline in bronchiolitis.
- Mechanism: improved mucociliary clearance.

N Engl J Med. 2006;354:241–50
JAMA Pediatr. 2014 Jul;168(7):657-63

Discussion

- First double blind placebo trial evaluating salt as a sole therapy in asthmatic children.
- Halotherapy with salt injection was associated with a statistical improvement in BHR and quality of life questionnaire in the short term.
- No improvement was observed in spirometry.
- No improvement was observed in FeNO values as indicator for airway inflammation.

Limitations

- Small sample size
- Salt aerosol concentration was not measured
- Control group stayed in a salt room with out salt injection- is it placebo?
- Mild asthma → not enough airway inflammation and little room for improvement
- Short term follow-up
- The primary outcome was MCT, adenosine challenge test may be more appropriate.
- The correlation between MCT and asthma is controversial.

A glance to the future

- Effect of halotherapy should be evaluated in larger cohort of children:

  - ✓ With moderate to severe asthma
  - ✓ As an additive to anti-inflammatory therapy
  - ✓ Benefits in longer terms

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Thanks!

- Prof. Bentur Lea
- Dr. Ronen Bar-Yoseph
- Dr. Galit Livnat
- Dr. Fahed Hakim
- Dr. Vered Nir
- Dr Moshe Rotschild
- Nir Kugelman Jr.

- Pediatric Pulmonary Institute – Moneera, Malake, Merav, Anna, Yahna, Nina