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Original Article

Sino nasal inhalation of isotonic versus hypertonic saline (6.0%) in CF patients with chronic rhinosinusitis — Results of a multicenter, prospective, randomized, double-blind, controlled trial

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Abstract

Background: Chronic rhinosinusitis is a hallmark of Cystic fibrosis (CF) impairing the patients' quality of life and overall health. However, therapeutic options have not been sufficiently evaluated. Bronchial inhalation of mucolytic substances is a gold standard in CF therapy. Previously,

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we found that sinonasal inhalation of dornase alfa as vibrating aerosol reduces symptoms of chronic rhinosinusitis more effectively than NaCl 0.9% (net treatment benefit: −5.87 ± 2.3 points, p = 0.017; SNOT-20 total score). This multicenter study compares the effect of NaCl 6.0% vs. NaCl 0.9% following the protocol from our preceding study with dornase alfa.

Methods: Sixty nine CF patients with chronic rhinosinusitis in eleven German CF centers were randomized to receive sinonasal vibrating inhalation of either NaCl 6.0% or NaCl 0.9% for 28 days. After 28 days of wash-out, patients crossed over to the alternative treatment. The primary outcome parameter was symptom score in the disease-specific quality of life Sino-Nasal Outcome Test-20 (SNOT-20). Additionally, pulmonary function was assessed, as well as rhinomanometry and inflammatory markers in nasal lavage (neutrophil elastase, interleukin (IL)-1β, IL-6, and IL-8) in a subgroup.

Results: Both therapeutic arms were well tolerated and showed slight improvements in SNOT-20 total scores (NaCl 6.0%: −3.1 ± 6.5 points, NaCl 0.9%: −5.1 ± 8.3 points, ns).

In both treatment groups, changes of inflammatory parameters in nasal lavage from day 1 to day 29 were not significant. We suppose that the irritating properties of NaCl 6.0% reduced the suitability of the SNOT-20 scores as an outcome parameter. Alternative primary outcome parameters such as MR-imaging or the quantity of sinonasal secretions mobilized with both saline concentrations were, however, not feasible.

Conclusion: Sinonasal inhalation with NaCl 6.0% did not lead to superior results vs. NaCl 0.9%, whereas dornase alfa had been significantly more effective than NaCl 0.9%.

Keywords: Hypertonic saline; Sodium chloride; Sino-Nasal Outcome Test-20; Rhinomanometry; Nasal lavage; Inflammation

1. Introduction

Cystic fibrosis (CF) is the most frequent life-shortening autosomal recessive disorder in the Caucasian population. The impaired mucus clearance promotes infections and alters function of many organs especially of the digestive and respiratory tracts including the lower and upper airways and paranasal sinuses. In general, CF patients exhibit both, chronic inflammation of the lower respiratory tract as well as chronic rhinosinusitis (CRS) [1–6]. The frequency and severity of ear–nose–throat (ENT) problems are reported by only 10% of the CF patients concerned by CRS [1] and are significantly underestimated by the attending physicians [4]. Indeed, almost 100% of CF patients exhibit morphological changes in computed tomography (CT) of the nose and paranasal sinuses [7]. Furthermore, it was shown, that the prevalence of rhinosinusitis is up to 63% [8] and the prevalence of nasal polyps is 50% in adult CF patients [9]. Only 7.1% of CF patients are free from inflammatory changes in sinonasal histology [10]. For the lower respiratory tract, the inhalation of mucolytic and antibiotic substances is the gold standard in CF therapy. In contrast, conventional inhalation therapy is not able to deposit relevant amounts of mucolytics or antibiotics in the paranasal sinuses [11]. Only pulsating aerosols (PARI Sinus™) facilitate a relevant deposition of nebulized drugs in the paranasal sinuses as shown by in vitro and in vivo scintigraphic studies [12–14]. Previously, we performed a study with sinonasal vibrating inhalation of recombinant DNAse (dornase alfa) as a mucolytic substance. We found that dornase alfa significantly reduces sinonasal symptoms (SNOT-20) in CF patients with CRS compared to NaCl 0.9% [15,16]. Small improvements were seen with NaCl 0.9%, which did not reach significance. By the usage of the identical study design, we aimed to assess in a next step, whether sinonasal inhalation with hypertonic saline (NaCl 6.0%) applied with vibrating aerosols reduces symptoms of rhinosinusitis in CF.

2. Methods

2.1. Trial design

The study was conducted as a multicenter, prospective, randomized, double-blind, controlled, cross-over trial (Fig. 1) applying the same protocol as in our previous trial on sinonasal inhalation of dornase alfa in CF patients [15,16]. Patients fulfilling the study criteria were enrolled in their attending CF center and randomized to inhale either hypertonic (NaCl 6.0%) or isotonic saline (NaCl 0.9%) once daily for 28 days. After a wash-out period of at least 28 days, patients crossed over to the alternative treatment. Subjects were examined at the beginning (V1, V3) and the end (V2, V4) of each period. Therapy with intravenous antibiotics within the wash-out-period delayed the start of the second period for another 28 days.

2.2. Participants

Participants were enrolled in eleven German CF outpatient clinics (Berlin, Frankfurt, Greifswald, Hamburg, Heidelberg, Jena, Leipzig, München, Münster, Tübingen, Würzburg). Patients aged at least six years with a confirmed diagnosis of CF (two positive sweat tests and/or genetic analysis) and with chronic symptoms of rhinosinusitis according to the criteria of the European Position Paper on Rhinosinusitis [17] were included.

Informed written consent was obtained from all patients and/or parental guardians. The study was approved by the local ethics committees and the Federal Institute for Drugs and Medical Devices (BfArM) and was registered at ClinicalTrials.gov (Identifier NCT01086839) in March 2010.

2.3. Interventions and outcomes

Sinonasal inhalation was performed using the PARI SINUS compressor (PARI GmbH, Starnberg, Germany) together with

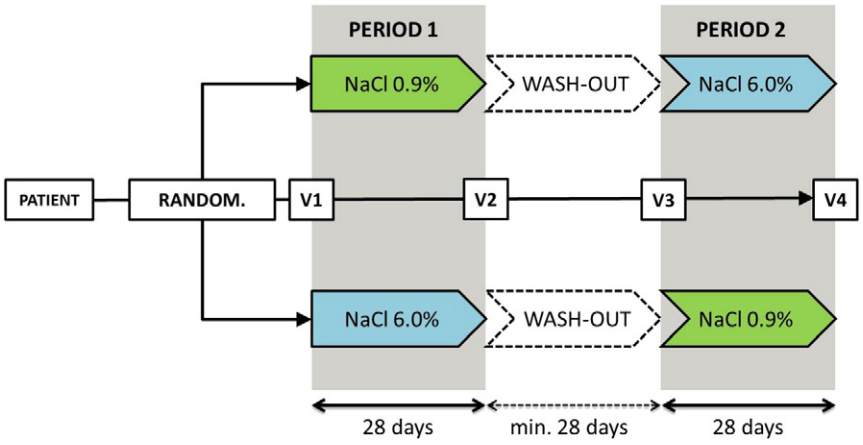

Fig. 1. Design of the study (Random = randomization, V = visit, min = minimum).

a PARI LC SPRINT SINUS nebulizer. NaCl 6.0% or NaCl 0.9% were aerosolized into one nostril, while the contralateral nostril was largely occluded and the soft palate elevated. Study medication (4 mL) was administered once daily, first to one nostril for 4 min and then to the other for a further 4 min. The total amount of study medication inhaled per session was approximately 1 mL per nostril (calculated on Total Output Rate of 220 mg/min).

From day 1 to day 28 (period 1) or day 57 to day 84 (period 2), participants nasally inhaled an ampoule NaCl 6.0% or NaCl 0.9% once daily (24 ± 2 h).

Primary outcome parameter was changes in the Sino-Nasal Outcome Test (SNOT-20, overall score). Secondary parameters included changes in primary nasal symptoms, secondary rhinogenous parameters, general quality of life, inflammatory parameters in nasal lavage (NL), and rhinomanometry.

2.4. Sino-Nasal Outcome Test-20 (SNOT-20)

SNOT-20 is a disease-specific, health-related, 20-item quality of life measure for patients with rhinosinusitis focusing on rhinogenous as well as on general discomforts. For the present study, a validated German adapted version was used. SNOT-20 scores range between 0 and 5 for each item, with higher scores indicating a greater health burden. The questionnaire includes four specific sections: (1) 'Total SNOT-20 score for all 20 items'; (2) 'Primary Nasal Symptoms' (PNS = nasal obstruction, sneezing, running nose, thick nasal discharge, reduced smelling); (3) 'Secondary Nasal Symptoms' (SNS = postnasal discharge, need to clear one's throat, cough, ear pressure, ear pain and facial pain/pressure) and (4) 'General Quality of Life' (GQL = dizziness, difficulty falling asleep, waking up at night, fatigue during daytime, reduced productivity, reduced concentration, frustrated/restless/irritable, a feeling of sadness and embarrassment). A minimum of 13 points in SNOT (excluding 'cough') was taken as inclusion criterion to facilitate a relevant improvement.

2.5. Nasal lavage (NL)

NL was performed by inserting 10 ml of sterile isotonic saline (0.9%) into each nostril with a 10 ml syringe. This was performed in accordance with the standard diagnostic procedure for nasal lavage [18]; head in a slightly reclined position and the soft palate occluded. A protease inhibitor (Protease Inhibitor Mix G, Serva, Germany) was added to the native NL and stored at −80 °C.

2.6. Immunological methods

Quantification of IL-1β, IL6 and IL8 in NL was done using a cytometric bead array (luminex technique): 25 μl NL were analyzed via High Sensitivity Kit (HSTCMAG-28SK-03, EMD Millipore).

Neutrophil elastase (NE) was determined using ELISA: 100 μL NL were analyzed in duplicate using the Polymorphonuclear (PMN) Elastase ELISA according to manufacturer's instructions (DEH3311, Demeditec Diagnostics GmbH).

2.7. Statistical methods

Data were analyzed with SAS 9.3 for Windows (version 6.1.7601). Open Clinica was used for data management (Community edition, version 3.0.4). All variables were described via adequate non-confirmatory statistics (number of patients, mean, and standard deviation). Values of visit 1, day 1 (period 1) and visit 3, day 57 (period 2) were used as baseline values. For the characterization of the study population (baseline data), values of visit 1, day 1 were used. An additional sensitivity analysis was performed to replace missing values for the primary endpoint only. The primary and secondary endpoints were analyzed using a mixed linear model on treatment differences (NaCl 6.0% versus NaCl 0.9%) with the fixed effects` sequence of treatments´ (NaCl 6.0%–NaCl 0.9% versus NaCl 0.9%–NaCl 6.0%) and 'period' (period 1 versus 2) and as random effect the patient nested in sequence (intention-to-treat-analysis). The significance level

was set at alpha = 0.05 (95% confidence intervals are shown). An additional post-hoc analysis (t-test, Bonferroni correction (factor 5, alpha = 0.01)) was done to consider treatment effects in SNOT total score and subscores separately for every treatment dose (alpha = 0.01).

3. Results

A total of 69 patients were enrolled between April 2010 and June 2013 (first subject in: 27/04/2010, last subject out: 05/06/2013). Fig. 2 illustrates the study process including the number of participants who were randomly assigned, who received one of the two sequences, who dropped out (with reasons), and who were analyzed for the primary outcome. Tables 1 and 2 summarize baseline data as well as the clinical characteristics of participants and findings in each of the study arms.

3.1. Primary outcome analysis

Patients treated with NaCl 6.0% showed a significant improvement in total SNOT score of 3.1 ± 6.5 points from day 1 (23.0 ± 10.4) to day 29 of treatment (20.7 ± 10.1). When treated with NaCl 0.9% a significant improvement in the SNOT score from day 1 (24.8 ± 11.0) to day 29 (19.4 ± 9.6) of 5.1 ± 8.3 points was shown. The estimator of the treatment effect is −1.71, 95% confidence interval (−4.21, 0.79). The difference between the two treatments is not significant ($F_{1.51}$ = 1.88, p = 0.18). The additional post-hoc analysis

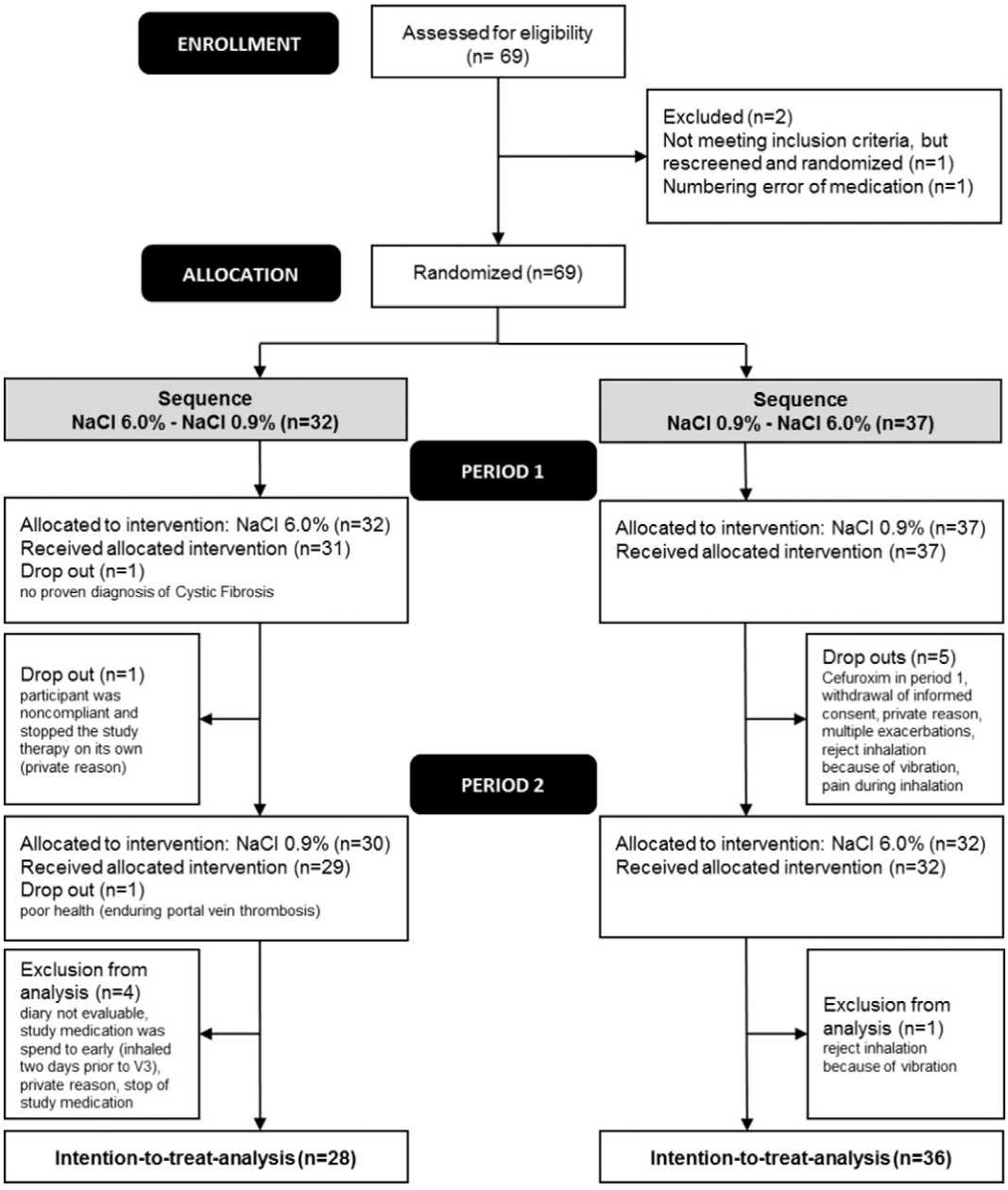

Fig. 2. Participant flow diagram.

Table 1
Demographic and clinical characteristics of study participants.

		Total	NaCl 0.9%–NaCl 6.0%	NaCl 6.0%–NaCl 0.9%
Subjects		69	37	32
Sex	Female	29 (42%)	16 (43%)	13 (41%)
Age	Mean age (years)	22.8 ± 12	22.5 ± 13.5	23.1 ± 10.3
Allergy	Yes	25 (37%)	12 (33%)	13 (42%)
Allergic rhinitis	Yes	14 (20%)	7 (19%)	7 (23%)
ABPA	Yes	3 (4%)	2 (5%)	1 (3%)
Chronic infections at baseline	Yes			
- *Pseudomonas aeruginosa*		23 (33%)		
- *Aspergillus fumigatus*		9 (13%)		
- *Candida albicans*		7 (10%)		
- *Achromobacter xylosoxidans*		3 (4%)		
- *Klebsiella oxytoca*		1 (2%)		
- *Pseudomonas alcaligenes*		1 (2%)		
- *Candida glabrata*		1 (2%)		
Genotype	Homozygous for F508del	26 (38%)		
	Heterozygous for F508del	31 (45%)		
	Other	7 (10%)		

showed significant treatment effects for both concentrations of saline. The analysis of the cross over design showed no significant sequence ($F_{1.65}$ = 0.56, p-value 0.46) or period effects ($F_{1.51}$ = 2.90, p = 0.095). Fig. 3 demonstrates the changes in all SNOT-20 items after 28 days of sinonasal inhalation with either NaCl 0.9% or NaCl 6.0%.

3.2. Secondary endpoints

PNS scores improved by 4.2 ± 13.6 points from day 1 to day 29 in patients treated with NaCl 6.0% (34.7 ± 14.1 to 31.9 ± 15.8). When treated with NaCl 0.9% an improvement of the PNS score from day 1 (36.5 ± 15.0) to day 29 (29.4 ± 15.9) of 7.0 ± 14.3 points was shown. The difference between the two treatments is not significant ($F_{1.51}$ = 1.41p = 0.24). The analysis of the cross-over design did not show significant sequence ($F_{1.65}$ = 2.43, p = 0.12) or period effects ($F_{1,51}$ = 0.71, p = 0.40). Patients treated with NaCl 6.0% showed an improvement in SRS scores from day 1 (22.8 ± 12.1) to day 29 (21.0 ± 13.6) of 2.7 ± 9.8 points. When treated with NaCl 0.9%, SRS scores improved by 3.4 ± 10.4 points from day 1 (24.9 ± 13.8) to day 29 (21.2 ± 12.9). The difference between the two treatments is not significant ($F_{1.51}$ = 0.08, p = 0.78). Patients treated with NaCl 6.0% showed an improvement of the GQL scores from day 1 (16.7 ± 13.4) to day 29 (14.3 ± 11.8) of 2.8 ± 8.8 points. When treated with NaCl 0.9% an improvement of the GQL score from day 1 (18.2 ± 13.8) to day 29 (12.7 ± 11.1) of 5.1 ± 9.9 points was shown. The difference between the two treatments is not significant ($F_{1.51}$ = 1.75, p = 0.19). The analysis of the cross over design revealed no sequence-($F_{1.65}$ = 0.02, p = 0.88) but a significant period effect ($F_{1.51}$ = 6.7, p = 0.013). Patients treated with either NaCl 6.0% or NaCl 0.9% showed a slight improvement of nasal airflow (inspiratory flow before decongestion) from day 1 to day 29.

Composite scores in each treatment arm are shown graphically in Fig. 4.

In both treatment groups, no significant changes of inflammatory parameters (NE, IL1β, IL6, and IL8) in NL from day 1 to day 29 were observed, although means of IL1ß and IL8 appeared to be somewhat lower after 28 days of sinonasal inhalation with hypertonic saline (Fig. 5).

3.3. Safety

Altogether, sinonasal inhalation of hypertonic and isotonic saline was well tolerated. Safety reports from 59 patients documented a total of 253 adverse events. Ten of the adverse events were classified as serious (three pulmonary exacerbations, diabetic imbalance, oesophageal varices bleeding, portal vein thrombosis, intravenous antibiotic therapy, viral gastroenteritis, thorax pain, port catheter implantation). Thirteen events were probably or very likely related to the interventions and a total of 86 events were considered to be possibly or doubtfully related. Adverse events classified as probable (NaCl 0.9%: N = 4, NaCl 6.0%: N = 3, washout: N = 1) or very likely (NaCl 0.9%: N = 5, NaCl 6.0%: N = 0, washout: N = 0) related to study medication were epistaxis, otalgia, pain during inhalation and pressure/burning pain in sinonasal segment. The remaining 167 events were not related to the study medication. Adverse events occurred almost equally in both treatment groups (NaCl 0.9%: N = 80, NaCl 6.0%: N = 74, washout/before start/after end: N = 99).

4. Discussion

This multicenter, prospective, randomized, double-blind, controlled trial was performed to assess the effects of hypertonic saline (NaCl 6.0%) vs. isotonic saline (NaCl 0.9%) inhaled as vibrating aerosol on sinonasal symptoms in CF patients suffering from CRS. CRS in CF is caused by impaired mucociliary clearance in the upper airway segment due to an enhanced viscosity of secretions. Hypertonic saline is a standard therapy for CF-related pulmonary involvement - based

Table 2
Summary of findings.

Hypertonic saline (NaCl 6.0%) compared to isotonic saline (NaCl 0.9%) with vibrating aerosol inhalation

Patients: CF patients with chronic rhinosinusitis
Settings: Multicenter, prospective, randomized, double-blind, controlled trial (12 German Cystic Fibrosis outpatient clinics)
Intervention: NaCl 6.0%
Comparison: NaCl 0.9%

Outcome	NaCl 6.0% (CI 95%)	Numbers analyzed	NaCl 0.9% (CI 95%)	Numbers analyzed
SNOT total score:				
Day 1 (Pt)	23.0 ± 10.4 (20.3–25.7)	59	24.8 ± 11.0 (22.0–27.5)	65
Day 29 (Pt)	20.7 ± 10.1 (18.1–23.3)[a]	62	19.4 ± 9.6 (17.0–21.8)[a]	65
Change(Pt)	−3.1 ± 6.5		−5.1 ± 8.3	
PNS score:				
Day 1 (Pt)	34.7 ± 14.1(31.0–38.4)	59	36.5 ± 15.0 (32.8–40.2)	65
Day 29 (Pt)	31.9 ± 15.8 (27.9–35.9)	62	29.4 ± 15.9 (25.4–33.3)[a]	65
Change (Pt)	−4.2 ± 13.6		−7.0 ± 14.3	
SRS score:				
Day 1 (Pt)	22.8 ± 12.1 (19.6–25.9)	59	24.9 ± 13.8 (21.4–28.3)	65
Day 29 (Pt)	21.0 ± 13.6 (17.6–24.5)	62	21.2 ± 12.9 (18.0–24.4)	65
Change (Pt)	−2.7 ± 9.8		−3.4 ± 10.4	
GQL score:				
Day 1 (Pt)	16.7 ± 13.4 (13.2–20.2)	59	18.2 ± 13.8 (14.8–21.6)	65
Day 29 (Pt)	14.3 ± 11.8 (11.3–17.3)	62	12.7 ± 11.1 (10.0–15.5)[a]	65
Change (Pt)	−2.8 ± 8.8		−5.1 ± 9.9	
FEV 1:				
Day 1 (%)	84.4 ± 22.7 (78.6–90.1)	62	82.0 ± 23.1 (76.1–87.8)	63
Day 29 (%)	84.4 ± 22.5 (78.6–90.2)	60	82.7 ± 23.2 (76.9–88.6)	63
Change (%)	0.04 ± 6.73		−0.3 ± 6.9	
Rhinomanometry:				
∑ Insp. flow before decongestion				
Day 1 (mL/s)	706.7 ± 349.1 (590.3–823.1)	37	694.8 ± 362.9 (568.2–821.4)	34
Day 29 (mL/s)	788.5 ± 334.5 (665.8–911.2)	31	812.1 ± 355.0 (686.2–938.0)	33
Change (%)	11.6		16.9	
∑ Insp. flow after decongestion				
Day 1 (mL/s)	1563.4 ± 988.1 (1207.2–1919.7)	32	1404.1 ± 890.5 (1058.8–1749.4)	28
Day 29 (mL/s)	1665.3 ± 1122.4 (1230.1–2100.6)	28	1763.8 ± 1116.0 (1354.4–2173.1)	31
Change (%)	6.5		25.6	

Values are given as mean ± standard deviation.
CF: Cystic Fibrosis.
CI: confidence interval.
SNOT: Sino-Nasal Outcome Test.
PNS: primary nasal symptoms.
SRS: secondary rhinogenous symptoms.
GQL: general quality of life.
∑ Insp. flow: sum of inspiratory flow of both nostrils.
Pt: POINTS.
NL: nasal lavage.
[a] Significantly different in comparison to day 1 (post-hoc analysis, $\alpha < 0.01$).

on the (1) reduction of viscosity and elasticity by a breakdown of ionic bonds of mucus, (2) rehydrating of secretions due to an increased osmotic flow of water into the mucus layer and (3) enhanced mucus clearance by building more compact mucin macromolecules [19]. As a principal result of the study, both concentrations of saline improved symptoms assessed with the well-established Sino-Nasal Outcome Test-20 (SNOT-20). These effects were more obvious after 28 days of sinonasal inhalation with NaCl 0.9%. Isotonic saline improved SNOT total score by −5.1 points while hypertonic saline only led to −3.1 points of improvement. Thereby, changes in SNOT total scores ≥5 points are considered as clinically relevant. This study shows that NaCl 6.0% is not superior to NaCl 0.9% regarding the treatment of sinonasal symptoms.

In our preceding trial, dornase alfa caused statistically and clinically benefits in CF patients with CRS: it improved total SNOT score by −7.1 points whereas isotonic saline improved symptoms by −1.3 points (difference: 5.9 points) [15]. Compared to the present study, the effects of hypertonic saline on sinonasal symptoms are much weaker than those of dornase alfa. We attribute this finding to the irritating properties of hypertonic saline on airway mucosa, which are well described

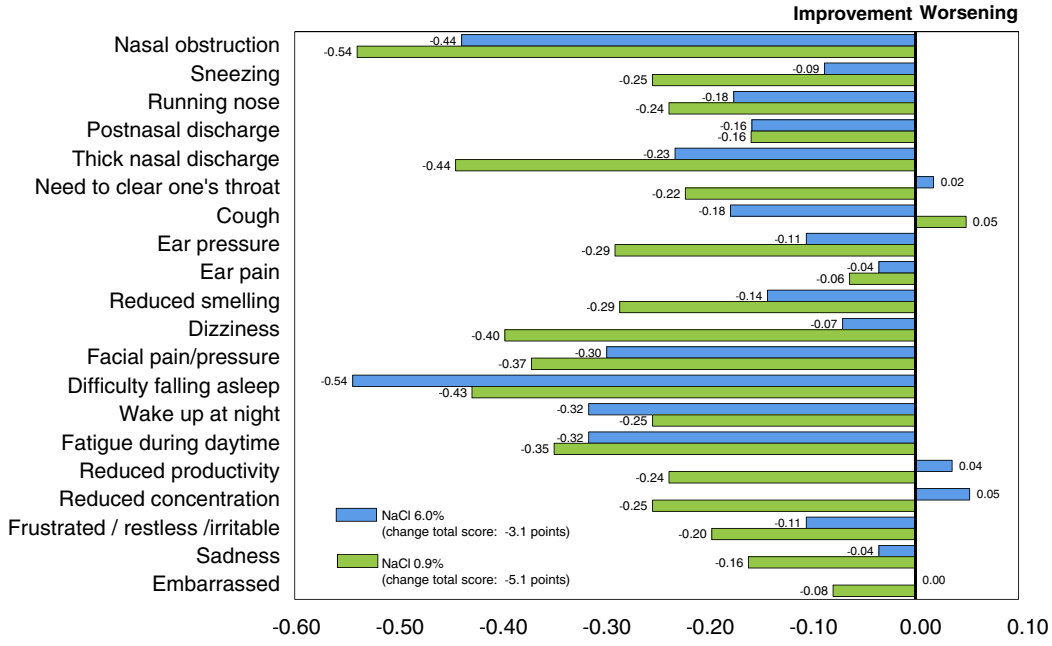

Fig. 3. Changes to SNOT-20 items after 28 days of sinonasal inhalation with either isotonic (NaCl 0.9%) or hypertonic (NaCl 6.0%) saline.

in trials assessing bronchial inhalation with hypertonic saline [20,21] where saline in concentrations from 6 to 7% provoked cough and airway obstructions. Elkins et al. showed by the means of a double-blind, parallel trial including 164 CF patients that adverse drug reactions were significantly more common in the hypertonic saline group (NaCl 7%) than in control

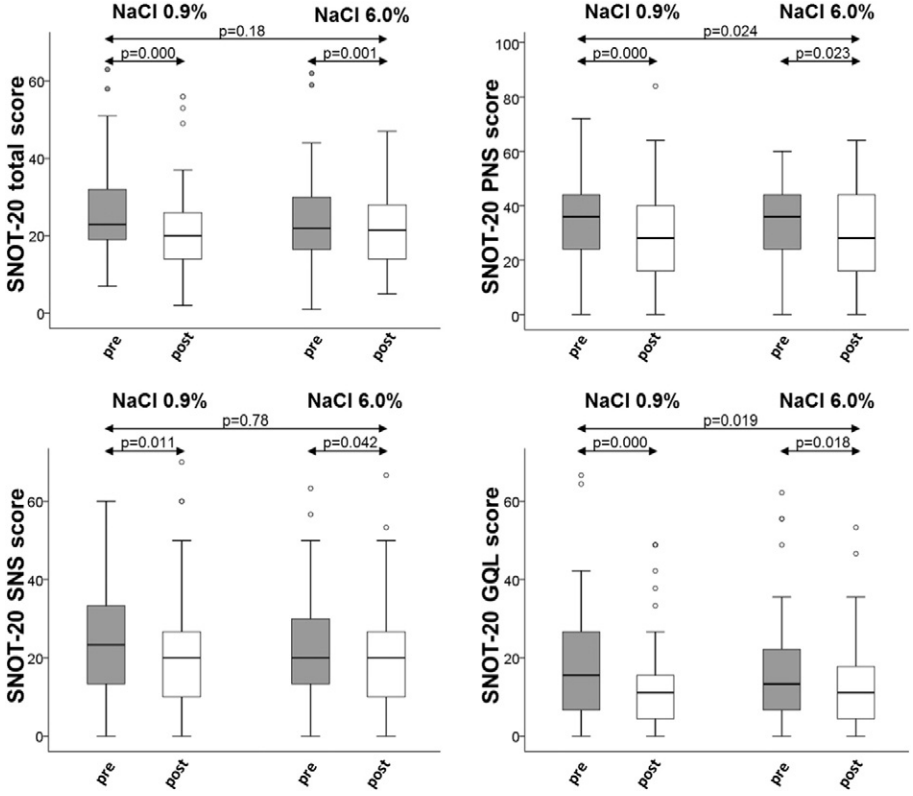

Fig. 4. Effects of sinonasal inhalation of hypertonic saline (NaCl 6.0%) and isotonic saline (NaCl 0.9%) on SNOT-20 subscores. (Sino-Nasal Outcome Test (SNOT-20): total score represents the sum of all 20 items. PNS (primary nasal symptoms) subscore includes nasal obstruction, sneezing, running nose, thick nasal discharge, reduced smelling. (SNS (secondary nasal symptoms) subscore includes postnasal discharge, need to clear one's throat, cough, ear pressure, ear pain and facial pain/pressure. GQL (general quality of life) subscore includes dizziness, difficulty falling asleep, waking up at night, fatigue during daytime, reduced productivity, reduced concentration, frustrated/restless/irritable, a feeling of sadness and embarrassment). The boxes extend from the 25th to 75th percentiles, the line in the middle of the box is the median, the whiskers go down to the 10th percentile/up to the 90th and points above the whiskers are outliers (alpha = 0.05).

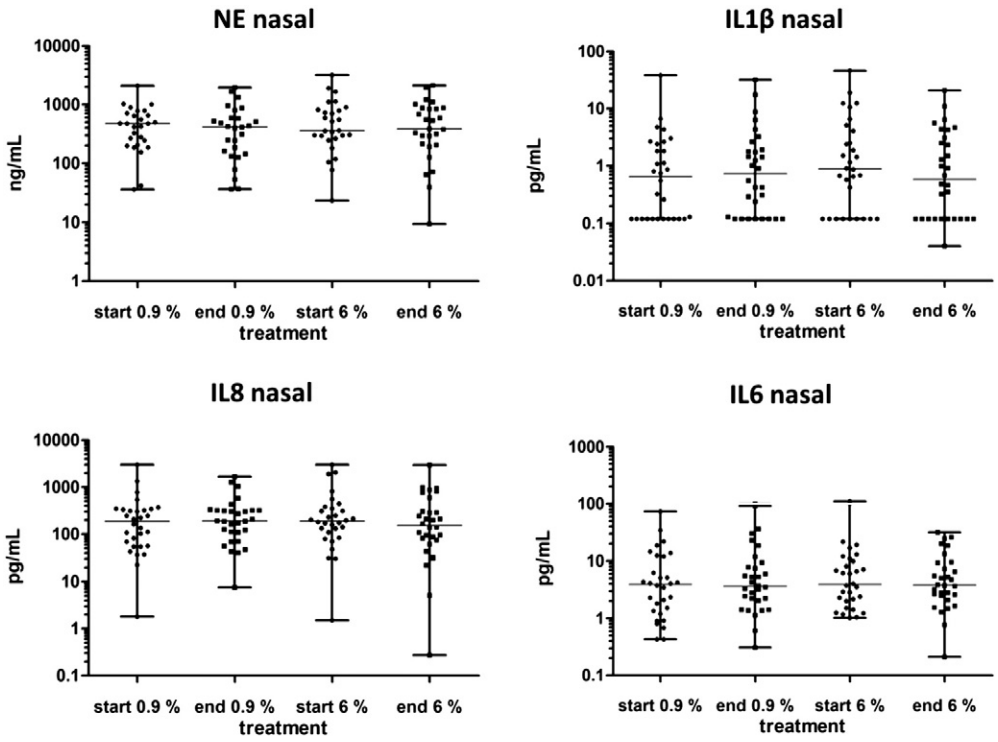

Fig. 5. Changes in cytokines in nasal lavage after 28 days of sinonasal inhalation with either isotonic (NaCl 0.9%) or hypertonic (NaCl 6.0%) saline (given as interquartile range with median, n = 27–30, NE: neutrophil elastase, IL: interleukin).

group (NaCl 0.9%) [21]. Nevertheless, due to improved lung function and reduced exacerbation rates, the authors concluded that 'hypertonic saline, preceded by a bronchodilator, is an inexpensive, safe, and effective additional therapy for patients with cystic fibrosis'. In the present study, adverse events classified as probable (NaCl 0.9%: N = 4, NaCl 6.0%: N = 3, washout: N = 1) or very likely (NaCl 0.9%: N = 5, NaCl 6.0%: N = 0, washout: N = 0) related to study medication were epistaxis, otalgia, pain during inhalation and pressure in sinonasal segment. Hence, one can derive from the adverse events that isotonic saline also exhibits irritant and pro-algesic properties in the UAW. Therefore, we must assume that SNOT-20 may have limitations to assess sinonasal symptoms on the basis of our study design [22,23]. To some extent the result of the primary outcome parameter was surprising: After the close-out of the study, many patients reported a very effective mobilization of mucus and crusts from the UAW segment for the study period in which they received hypertonic saline. Thereby, therapeutic effect of mucolytic might not be adequately reflected in the subjective perception of SNOT-20 scores. Objective measures like `quantification of mobilized amounts of mucus´ would have been a particularly interesting outcome parameter. However, most of the secretions mobilized from the nose and paranasal sinuses drain physiologically as postnasal drip [24] and are swallowed, or to a much lower proportion expectorated, after reaching the pharynx. Therefore, quantification and comparison of secretions drained from the UAW appears to be almost impossible in a clinical trial involving CF patients. Two reasons prompted us to choose the SNOT-20 as the primary outcome parameter: first, the score – which is widely used for evaluation of conservative and surgical interventions in patients with rhinosinusitis – was successfully applied in our preceding trials applying dornase alfa and tobramycin to paranasal sinuses with the same vibrating nebulizer [15,25]. Secondly, serial MR-Imaging of sinonasal ventilated spaces as an alternative would have been interesting but costs to perform four sinonasal MRI in each of the 69 patients (276 MRI scans) by far exceeded our financial means.

As a second outcome parameter nasal patency was examined via active anterior rhinomanometry in a subgroup of patients. This technique allows the measurement of the inspiratory and expiratory flow and resistance of the nose. Sinonasal therapy might increase nasal patency by reducing mucosal swelling and by a higher fluidity of nasal secretions and mobilization of crusts. Patients treated with either NaCl 6.0% or NaCl 0.9% showed small improvements of nasal airflow, whereas NaCl 0.9% seemed to be slightly more effective without reaching statistical significance in comparison to hypertonic saline. Indeed, there was no need and no potential for improving nasal patency since mean total nasal inspiratory flow was within the normal range. To acquire data on mucosal swelling, polyps, and secretions, imaging techniques such as computed tomography or the more expensive but radiation free magnetic resonance tomography would be required. The latter radiation-free method is quite interesting for longitudinal studies on ventilation of UAW.

Furthermore, no alterations of inflammatory parameters (NE, IL1β, IL6, and IL8) in NL were observed. Previously it had been shown that hyperosmolar environments induce a histamine release from mast cells and basophils in vitro

and inflammatory mediators (histamine, TAME esterase, immunoreactive leukotriene) in vivo [26]. Additionally, van der Vaart et al. demonstrated in a study including 16 healthy intermittent smokers that repeated sputum inductions with hypertonic saline (NaCl 4.5%) induced/provoked a neutrophilic and a prolonged eosinophilic inflammatory response – IL8 increased significantly as well [27]. Gräber et al. investigated the effects of hypertonic saline on airway inflammation in a betaENaC-overexpressing mouse model for chronic obstructive lung disease and found that inhalation of hypertonic saline triggers proinflammatory stress (osmotic stress response) which may limit the therapeutic benefits of the treatment and require an adjunct anti-inflammatory strategy. For sinonasal inhalation, the results of cytokine analysis did not indicate proinflammtory effects of hypertonic saline [28]. In conclusion, a study on CRS in CF comparing dornase alfa, isotonic and hypertonic saline at concentration 3 and 6% with an imagine technique as main outcome parameter would be very interesting. For clinical practice we can conclude, that sinonasal inhalation of both iso- and hypertonic saline is a safe adjunct therapy for CF patients with CRS.

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Conflict of interest

All authors confirm that they are not involved in any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in this manuscript.

Contributors

Principal investigator: JGM. Design and realization of study: JGM, KS, JH, CK, AK, JR, FP, OS, BW, DS, WG, RF, JFB. Performed the experiments: JH, CA. Analyzed the data: JGM, US, JH, CA. Wrote the paper: JGM, CA.

Ethics approval

The trial was approved by the local Ethics Committee (vote number: 2720–12/09).

Registration

The trial has been registered at ClinicalTrials.gov. (Identifier NCT01086839) in March 2010.

Patient consent

Obtained.

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