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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