Running title: Xyloglucan-based nasal spray for rhinosinusitis

TYPE OF ARTICLE: ORIGINAL CONTRIBUTION

A randomized controlled trial comparing a xyloglucan-based nasal spray with saline in adults with symptoms of rhinosinusitis

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SUMMARY

***Background**:* This study assessed the efficacy, safety and tolerability of a xyloglucan-based nasal spray in the treatment of symptoms of rhinosinusitis.

***Methodology**:* In this randomized, double-blind study, 40 patients with rhinosinusitis, itching, nasal congestion or continuous sneezing and a Total Nasal Symptom Score (TNSS) of ≥8 were randomized to 2 weeks' treatment with a xyloglucan-based nasal spray ('xyloglucan') or a physiological saline nasal spray ('saline'). Assessments included the TNSS, rhinosinusitis severity index, nocturnal awakenings, use of rescue medication, safety and tolerability.

***Results**:* Baseline symptom scores were similar between groups. At treatment end, improvements from baseline were observed in both groups for TNSS (xyloglucan 58%; saline 35%, both $p<0.05$) and number of nocturnal awakenings ($p<0.05$). A significant improvement in the rhinosinusitis severity index was observed only with xyloglucan ($p<0.05$). At treatment end, mean [SD] scores were significantly lower in the xyloglucan group versus saline group for TNSS (3.60 [2.16] *vs* 5.40 [2.64], $p<0.05$) and rhinosinusitis severity index (7.55 [1.19] *vs* 6.45 [1.40], $p<0.05$), rhinorrhoea and itching (both $p<0.05$). No rescue medication was used. Both treatments were well tolerated.

***Conclusions**:* A xyloglucan-based nasal spray provided greater relief of rhinosinusitis symptoms than a physiological saline spray and was well tolerated.

<<Maximum allowed 200 words. Currently 197>>

Key words: nasal spray, rhinitis, rhinosinusitis, saline, xyloglucan

INTRODUCTION

Rhinosinusitis, or inflammation of the nose and paranasal sinuses, is a common disorder. It is estimated that 6–15% of the general population is affected by acute rhinosinusitis[1] and 5–13% by chronic rhinosinusitis[2]. A number of factors are implicated in the pathogenesis of rhinosinusitis, including viral and bacterial infections, allergy, anatomical abnormalities such as a deviated septum, ciliary impairment, tobacco smoking, and environmental factors such as dampness and air pollution[1]. Abnormalities of the sinonasal epithelial barrier and mucocilliary clearance may be of particular relevance in the pathogenesis of chronic rhinosinusitis[3].

Rhinosinusitis can cause a variety of symptoms, including nasal congestion, nasal discharge, facial pain or pressure and a reduced sense of smell[1]. The main treatment options include analgesics, decongestants, nasal saline irrigation and topical intranasal steroids[1,2]. Antibiotics may be indicated for bacterial infections, and antihistamines and allergen immunotherapy for allergic rhinitis[1,2].

While nasal saline irrigation is the most widely recommended nonpharmacological topical treatment, other options include nasal sprays incorporating substances such liposomes or cellulose that create a hydrofilm mechanical barrier to protect the nasal epithelium from allergens and irritants[2,4].

A new xyloglucan-based rhinological solution has been developed that contains physiological saline solution, methylsulfonylmethane and tamarind seed extract. The tamarind tree (*Tamarindus indica*) seed extract contains xyloglucan, which forms a protective biofilm over the sinonasal epithelium. We performed a clinical trial to compare the efficacy, safety and tolerability of the xyloglucan-based nasal spray with physiological saline nasal spray in the treatment of the clinical symptoms of rhinosinusitis.

MATERIALS AND METHODS

Study population

The study enrolled otherwise healthy Caucasian men and women aged >16 years who had at least one of the following symptoms: rhinosinusitis, itching, nasal congestion or continuous sneezing. Participants had to have a Total Nasal Symptom Score (TNSS) of ≥8. Patients were excluded if they had nasal polyps or nasal septum malformations that would compromise administration of the nasal spray, or had serious respiratory tract disease or other serious diseases that substantially reduced life expectancy. Patients who may not have been able to cooperate fully with study requirements, such as those with drug or alcohol addiction, were also excluded. Pregnant and breastfeeding women, and anyone who had participated in another clinical trial within 6 months were not eligible to participate.

Study design and procedures

This was a randomized, double-blind, controlled, parallel group study conducted at the Otorhinolaryngology Department of the 'SS. Fillippo eNicola' Hospital in Avezzano (AQ), Italy between March 2015 and March 2016. Patients were randomly assigned 1:1 to receive either a xyloglucan-based nasal spray (Rhinosectan) or a physiological saline nasal spray for 2 weeks, each administered as two sprays per nostril four times daily, at the same times each day. Treatment allocation was determined by a randomisation list generated automatically using NCSS PASS 2011 software. The spray devices containing the two study medications were physically indistinguishable and labelled as 'Device A' or 'Device B' plus the patient's randomisation number. Blinding codes were kept in sealed envelopes.

The Rhinosectan nasal spray contained a xyloglucan-based rhinological solution comprising physiological saline solution, methylsulfonylmethane and tamarind seed extract. The comparator spray contained physiological saline solution. The nasal sprays met the essential requirements for medical devices specified in Directive 93/42/EEC. The medication was administered by the patients, who were instructed to apply two 2-second sprays per nostril in a vertical position. The first administration was performed in the presence of the investigator, who ascertained that the correct technique was being used. Concomitant medications with a possible clinically significant effect on the upper respiratory tract, including on rhinosinusitis, were not allowed.

Patients attended three visits: screening (baseline), randomisation (Day 1), and end of treatment (Day 15), and had telephone follow-up contact after 1 month. At the screening visit, assessments included a medical history, evaluation of rhinosinusitis and associated symptoms (TNSS, rhinosinusitis severity index and number of nocturnal awakenings), a physical examination and safety laboratory tests. On Day 1 (which was no more than 14 days after the screening visit), participants were randomly assigned to a treatment group, began treatment and, after the first dose, completed the Nasal Sensory Spray Scale (NSSS) tolerability questionnaire. On Days 1 to 14, patients administered study treatment and completed a daily diary recording the time of administration, any adverse events, any emergency medications used and the number of nocturnal awakenings. At the end-of-treatment visit, symptoms (TNSS, rhinosinusitis severity index) and spray tolerability (NSSS) were evaluated, safety laboratory tests were performed and the daily diaries (including information on nocturnal awakenings) were collected.

The primary endpoints were: (1) TNSS at baseline and at end of treatment (the sum of the severity of the four nasal symptoms of congestion, rhinorrhoea, sneezing and itching, with the severity evaluated using a 4-point Likert scale [none, mild, moderate, severe][(5)]; (2) rhinosinusitis severity index at baseline and end of treatment (measured

by means of a 100-mm visual analogue scale [VAS], with patients asked to indicate their perception of the severity of their symptoms, from none to very serious); (3) the average number of nocturnal awakenings at baseline and end of treatment; and (4) the number of emergency rescue medications used. Secondary endpoints included: adverse events; vital signs and laboratory parameters; and sensory tolerability indices (smell, immediate taste, after-taste, liquid flowing into the throat, leakage of liquid from the nose, soothing sensation, urgency of sneezing and nasal irritation) assessed using the NSSS questionnaire, which comprises 13 questions, each of which is answered using a 7-point Likert scale (where 0=absent/more positive response, 6=present/more negative response, and 3=neutral response)[6].

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (amended version of 2008, Seoul) and complied with the guidelines for Good Clinical Practice and the rules and guidelines applicable to medical devices (UNI EN ISO 14155:2012, guideline MED DEV 2.7/4 of December 2010 "Guidelines on Clinical Investigation"). Ethical approval was obtained from the relevant Independent Ethics Committee. All participants provided written informed consent; both parents signed the consent form for participants aged less than 18 years.

Statistical analysis

Differences in the TNSS and rhinosinusitis severity index between treatment groups at baseline and the end-of-treatment visits were analysed using the Student's *t*-test. Individual symptoms (congestion, rhinorrhoea, sneezing, itching) were also analysed for each group. Between-group differences in the percentage of patients who used emergency medications and the percentage of nocturnal awakenings were analysed using the Chi-square test. Differences in the frequency of adverse events between the groups were analysed using Fisher's exact test. The presence or absence of clinically significant differences in vital signs or laboratory parameters (as evaluated by the

investigator) were analysed using the Student's *t*- test. NSSS results were analysed for each group using parametric and non-parametric tests as appropriate.

Analyses were performed on the intention-to-treat population (all randomized patients). The last-observation-carried-forward strategy was used in the event of missing data. $P<0.05$ was considered significant. All statistical analyses were carried out using IBM SPSS 22 for Windows.

The planned sample size was of 80 patients (40 per group) but could not be reached during the stipulated timeframe of the clinical trial, and so the results for the first 40 patients (20 per group) are presented here.

RESULTS

Forty patients were screened for the study, all of whom were subsequently randomized to treatment. All 40 patients completed the study, and all 40 were included in analyses. Two patients aged under 16 years were enrolled; since the study devices are not contraindicated for minors it was decided to accept their inclusion.

Demographics and baseline characteristics are summarised in Table 1. Just over half of participants were male (n=21; 52.5%) and mean age of participants was 46 years. Treatment groups did not differ with respect to age, body mass index or blood pressure. Thirty-six patients (90%) returned their daily diaries; all 36 had been compliant with treatment based on their diary entries (i.e. administered at least 2 sprays per nostril at least twice daily during the treatment period).

Efficacy

At baseline, there were no significant differences between treatment groups in terms of mean TNSS, rhinosinusitis severity index and number of nocturnal awakenings (Table 2). Severity scores for individual nasal symptoms also did not differ between groups (data not shown).

At the end of treatment, efficacy parameters had improved in both groups compared with baseline. Statistically significant improvements were observed in both groups for the TNSS (Table 2, Figure 1) and number of nocturnal awakenings (Table 2, Figure 2). TNSS improved by 58% in the xyloglucan-based-spray group compared with 35% in the physiological saline group (both $p<0.05$ versus baseline). The mean (standard deviation) number of nocturnal awakenings decreased from 1.60 (1.93) to 0.70 (1.46) in the xyloglucan-based-spray group and from 1.05 (1.40) to 0.65 (1.09) win the

physiological saline group (both $p<0.05$). More patients in the xyloglucan group than saline group reported the absence of nocturnal awakening from baseline to end of treatment (Table 2). Improvement from baseline in the rhinosinusitis severity index was significant only in the xyloglucan group ($p<0.05$; Table 2, Figure 3). No patient in either group used any rescue medication during the treatment period.

In the group treated with the xyloglucan-based spray, an improvement of more than 40% compared with baseline was observed for all four individual nasal symptoms, whereas only sneezing improved to this extent in the physiological saline group (Figure 4). In terms of the proportion of patients experiencing specific symptoms, decreases tended to be greater in the group who received the xyloglucan-based spray (Table 2); of note, the number of patients in the xyloglucan group who reported itching halved from baseline to end of treatment.

In terms of between-group differences, the TNSS and rhinosinusitis severity index were significantly lower in the xyloglucan group than saline group at the end of treatment (both $p<0.05$; Table 2, Figure 1). The number of nocturnal awakenings did not differ significantly between groups at the end of treatment (Table 2, Figure 2). Scores for individual nasal symptoms tended to be better in the xyloglucan group than saline group at the end of treatment, but the difference achieved statistical significance only for rhinorrhoea and itching (both $p<0.05$, Figure 5).

Safety and tolerability

Both treatments were generally well tolerated. No serious adverse events occurred. Overall, three patients in the physiological saline group reported 11 adverse events and five patients in the xyloglucan-based-spray group reported 22 adverse events. Most adverse events were mild in nature, and only two (dry nostrils, reported by one patient in each group) was considered to be possibly related to study treatment. The

most frequent adverse events were sneezing (four events in the xyloglucan-based-spray group versus one in the physiological saline spray group), dry cough (3 versus 0), lack of sleep (3 versus 0), dry nose (2 versus 1) and cough plus sore throat (0 versus 3). No clinically significant changes in vital signs or laboratory parameters occurred.

Patient satisfaction

Based on the results of the NSSS questionnaire, patients in both groups were generally satisfied with the sensory attributes of the treatment and device they received. After the first treatment administration, the level of satisfaction was at least 80% for all parameters in the xyloglucan-based-spray group and at least 75% in the physiological saline group, with the exception of "soothing sensation", for which the level of satisfaction was only 35% and 20%, respectively. The picture was similar at the end-of-treatment assessment, when the level of satisfaction was at least 85% for all parameters in the xyloglucan-based-spray group and at least 80% in the physiological saline group, with the exception of "soothing sensation" (both 40%).

DISCUSSION

Nonpharmacological treatments, used alone or as adjunctive therapy, are one of the options for the management of patients with rhinitis and rhinosinusitis[2]. One example is topical therapy with a saline solution[1,2,7]. The exact mechanism of action of saline solutions is not clear, but they may thin and clear mucus, remove antigens and inflammatory mediators, and improve mucociliary function[8,9]. Another nonpharmacological approach is to employ measures that create a mechanical barrier over the sinonasal mucosa, with the aim of reducing contact between allergens, irritants or pathogens and the mucosa[2,4]. Nasally applied cellulose powder (which hygroscopically takes up water to form a gel on the mucosa)[10-13] and lipid microemulsions[14-16] have been shown to reduce the symptoms of allergic rhinitis in double-blind, placebo-controlled studies, while an observational study has provided preliminary evidence of efficacy for a liposomal nasal spray[17].

The current study evaluated a nasal spray containing a xyloglucan-based rhinological solution that is designed to form a protective biofilm over the sinonasal mucosa. After two weeks of treatment, the xyloglucan-based spray reduced rhinorrhoea, itching, TNSS and the severity of rhinosinusitis significantly compared with a physiological saline nasal spray. One caveat is that, although the rhinosinusitis severity level was statistically significantly lower in the xyloglucan-based-spray group compared with the saline group at the end of treatment, this may not represent a clinically significant difference, given that, overall, patients had not reported severe rhinosinusitis at baseline.

The comparator nasal spray, physiological (isotonic) saline, is not a true placebo. It is known that saline solutions can provide symptom relief for patients with rhinosinusitis, and systematic reviews and meta-analyses have confirmed that nasal saline irrigation is effective in rhinosinusitis and allergic rhinitis[8,18,19]. However, one study found that a saline spray was less effective than irrigation[20] and guidelines

generally recommend saline irrigation rather than saline sprays[1,7]. Nonetheless, several studies have found that saline nasal sprays can provide some symptom relief[20-24]. The results of our study support this observation, with a reduction from baseline in the TNSS and number of nocturnal awakenings noted in the saline group. The xyloglucan-based spray also contains physiological saline; however, significant differences between the two preparations in favour of the xyloglucan-based spray suggest that the differences can be attributed to the xyloglucan component.

Both treatments were well tolerated. Most adverse events were related to the upper respiratory tract and were mild in severity. In addition, patients reported being generally satisfied with the sensory attributes of the xyloglucan-based spray, suggesting that it was not unpleasant to apply.

The main limitations of the study are the small sample size and short treatment period. Confirmation of the findings in a larger study is warranted. In addition, further evaluation of the efficacy and tolerability of the spray over a longer period of time may be informative. In the future, comparisons with saline nasal irrigation, as opposed to saline spray, and with different barrier-enforcing measures, would provide additional information about the comparative effectiveness of nonpharmacological therapeutic options for rhinosinusitis.

In conclusion, this study provides preliminary evidence that a xyloglucan-based nasal spray provides greater overall relief of the symptoms of rhinosinusitis than a physiological saline spray and is well tolerated.

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AUTHORSHIP CONTRIBUTION

All authors contributed significantly to the conception, design or execution of the study. All authors participated in drafting, reviewing and/or revising the manuscript, and all have approved its submission.

CONFLICT OF INTEREST

No conflicts of interest.

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TABLE AND FIGURE LEGENDS

Table 1 Demographics and baseline characteristics

Table 2 Total nasal symptom score, severity of rhinosinusitis and number of nocturnal awakenings at baseline and at the end of treatment

Figure 1 Mean Total Nasal Symptom Score at baseline and end of treatment

Figure 2 Mean number of nocturnal awakenings at baseline and end of treatment

Figure 3 Mean rhinosinusitis severity index at baseline and end of treatment

Figure 4 Percentage improvement in individual nasal symptom scores from baseline to end of treatment

Figure 5 Individual nasal symptoms at the end of treatment

Table 1 Demographics and baseline characteristics

	Physiological saline spray (n=20)	**Xyloglucan-based spray (n=20)**
Gender (M:F)	11/9	10/10
Age	43.6 (17.31)	49.3 (17.99)
Body mass index	24.8 (3.55)	26.7 (4.80)
Systolic blood pressure	119.5 (12.24)	115.8 (20.54)
Diastolic blood pressure	70.0 (7.26)	69.2 (10.45)

Values are mean (standard deviation).

$p>0.05$ for all comparisons between groups.

Figure 1 Mean Total Nasal Symptom Score at baseline and end of treatment

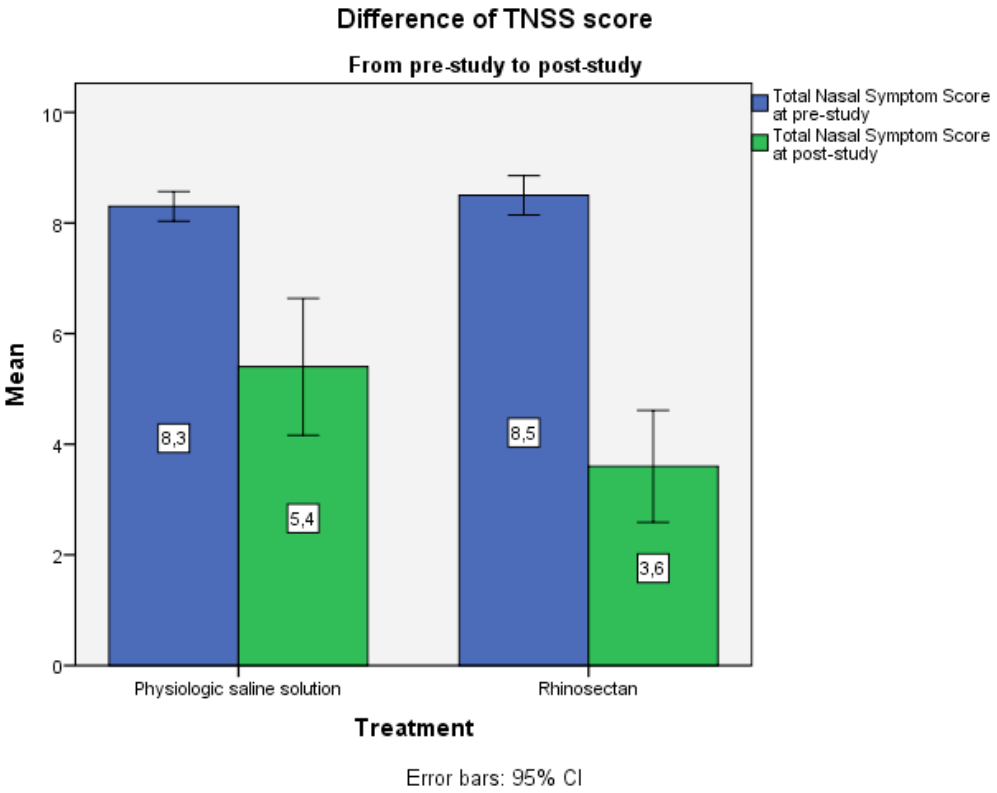

Figure 2 Mean number of nocturnal awakenings at baseline and end of treatment

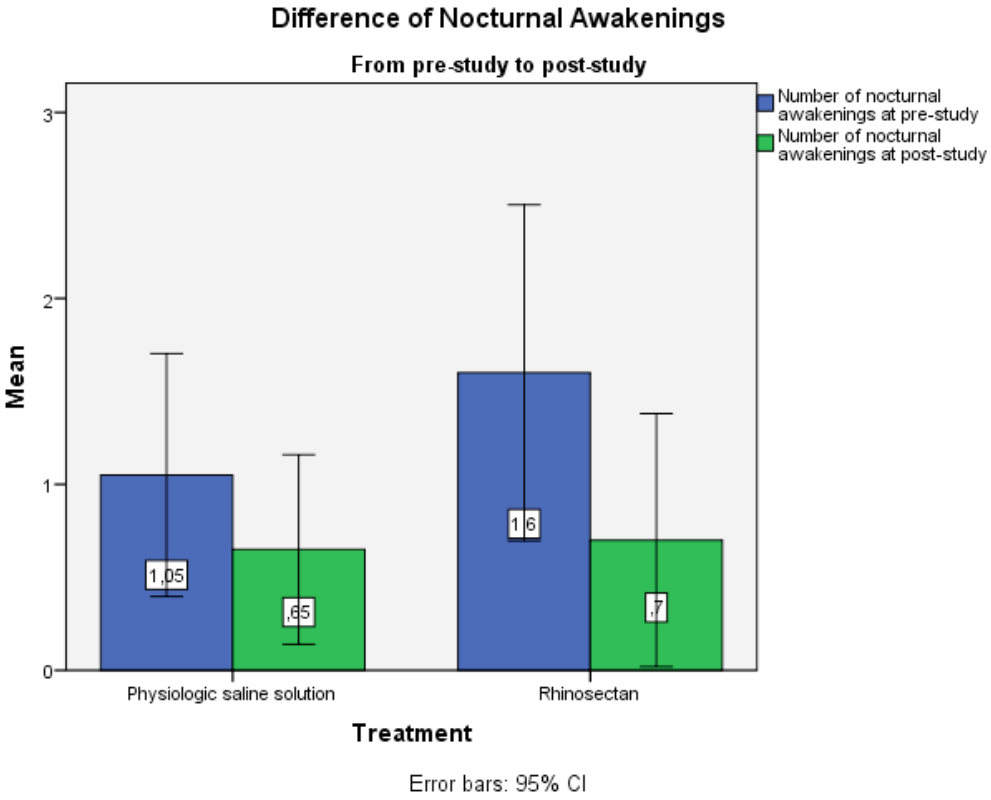

Figure 3 Mean rhinosinusitis severity index at baseline and end of treatment

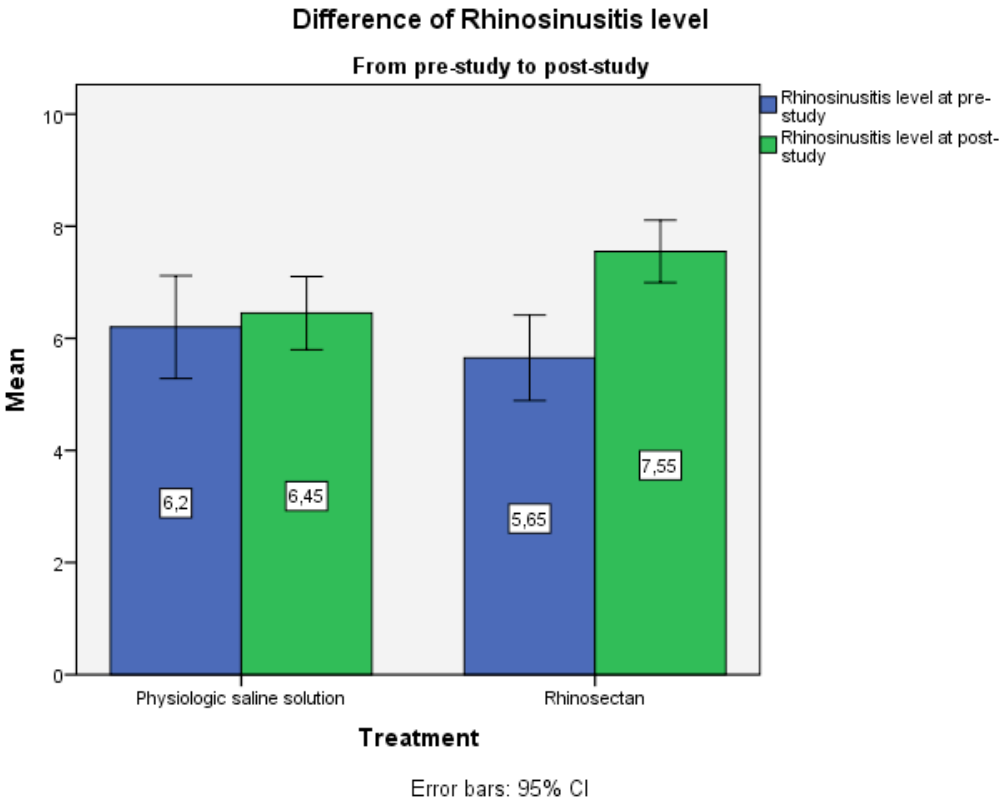

Figure 4 Percentage improvement in individual nasal symptom scores from baseline to end of treatment

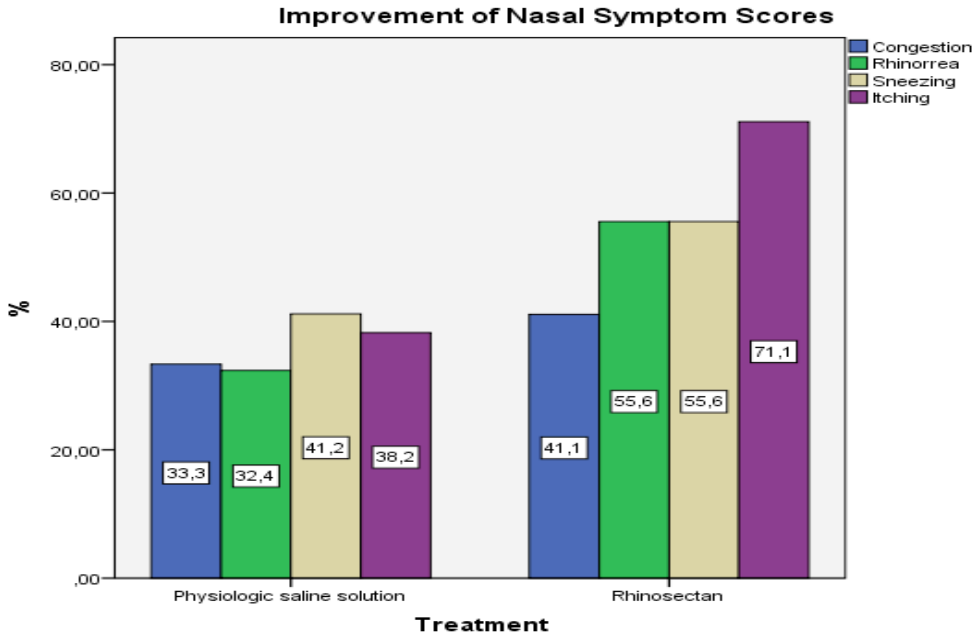

Figure 5 Individual nasal symptoms at the end of treatment

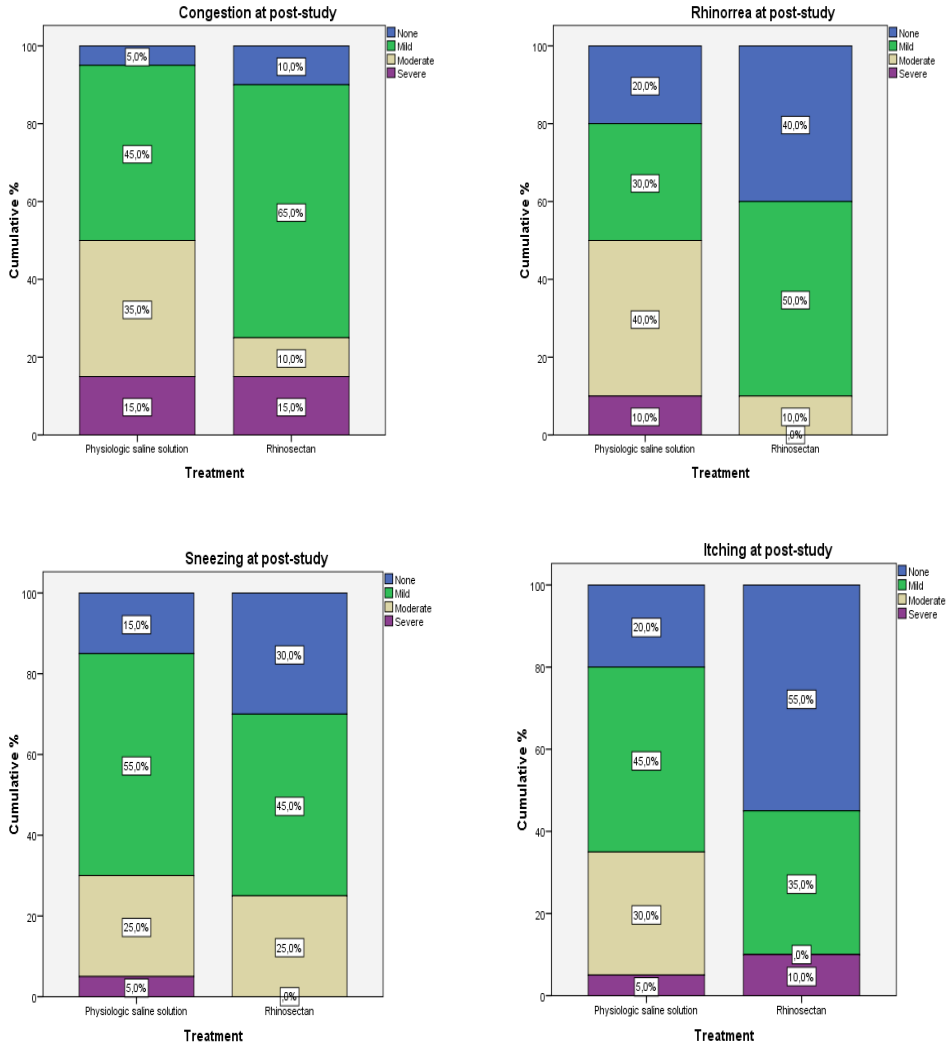

Table 2 Total nasal symptom score, severity of rhinosinusitis and number of nocturnal awakenings at baseline and at the end of treatment

		Physiological saline spray (N=20)	**Xyloglucan-based spray (N=20)**
Total Nasal Symptom Score[a]	Baseline	8.30 (0.57) [range 8–10]	8.50 (0.76) [range 8–11]
	End of treatment	5.40 (2.64)* [range 0–9]	3.60 (2.16)*† [range 0–8]
Patients with congestion, n (%)	Baseline	20 (100)	20 (100)
	End of treatment	19 (95)	18 (90)
Patients with rhinorrhoea, n (%)	Baseline	19 (95)	17 (85)
	End of treatment	16 (80)	12 (60)
Patients with sneezing, n (%)	Baseline	20 (100)	20 (100)

	End of treatment	17 (85)	14 (70)
Patients with itching, n (%)	Baseline	18 (90)	18 (90)
	End of treatment	16 (80)	9 (45)
Rhinosinusitis severity index[b]	Baseline	6.20 (1.96) [range 3–9]	5.65 (1.63) [range 3–9]
	End of treatment	6.45 (1.40)	7.55 (1.19)*[†]
Number of nocturnal awakenings[c]	Baseline	1.05 (1.40) [range 0–5]	1.60 (1.93) [range 0–6]
	End of treatment	0.65 (1.09)*	0.70 (1.46)*
Patients with nocturnal awakening, n (%)	Baseline	9 (45%)	11 (55%)
	End of treatment	7 (35%)	6 (30%)

Values are expressed as mean (standard deviation) unless indicated otherwise.

a Total Nasal Symptom Score = sum of the severity of congestion, rhinorrhoea, sneezing and itching, with severity evaluated using a 4-point Likert scale [none, mild, moderate, severe].

b Measured using a 100-mm visual analogue scale.

c Number of nocturnal awakenings per night.

* $p<0.05$ versus baseline.

† $p<0.05$ versus physiological saline spray at end of treatment.