ORIGINAL STUDY

Relief of nasal symptoms in obstructive rhinopathy with and without rhinosinusitis, with the SILSOS® hyper medical device. A randomized, double-blind, active comparator (saline)-controlled clinical trial

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ABSTRACT

BACKGROUND. Nasal obstruction is a primary symptom of common upper respiratory tract disorders, including common cold and acute and chronic rhinosinusitis with/without nasal polyposis. In patients affected by sinonasal diseases, transudation and edema are reported to increase and thicken the periciliary layer impairing the mucociliary clearance (MCC) and/or the mucociliary transport time (MCTt) which are preventative mechanisms against the deposition of inhaled, pro-inflammatory particulate matter as well as the harboring of infections at the level of paranasal sinuses. In clinical practice and in several nasal affections nasal saline solutions are always recommended for the cleansing of nasal cavities and relieving nasal symptoms.

MATERIAL AND METHODS. A randomized, double-blind, active comparator (isotonic, nasal saline solution) controlled, parallel study was conducted to evaluate the safety and the efficacy of SILSOS® hyper (a new Medical Device - MD - composed of the synergistic association of the patented silver salt Silver Sucrose Octasulfate and Potassium Sucrose Octasulfate) in patients suffering from obstructive rhinopathy, with nasal obstruction/congestion of moderate severity persistent since at least 10 days in advance of recruitment with/without rhinosinusitis.

At baseline (T0), ten days (T10) and twenty days (T20) after saline or SILSOS® treatment, study participants were evaluated subjectively with VAS and SNOT-22, and objectively by Active Anterior Rhinomanometry (AAR) and MCC/MCTt determination by means of the charcoal+3% saccharine test. All the patients were followed-up 30 days after the end of the treatment by a phone interview aimed to evaluate the long term effectiveness of the treatment.

RESULTS. All the 50 enrolled outpatients (aged 18-70 years) completed the study. The AAR analysis showed that whereas saline resulted ineffective on improving inspiratory and expiratory flow at any study timepoint, MD patients progressively and significantly ($p<0.05$) ameliorated in expiratory flow, at T0-T10 as well over the whole study period (T0-T20). Considering MCC and MCTt determination, no improvement in MCTt was observed over the 20 days study period. As the MCC is concerned, the mean values significantly improved at T20 ($p<0.0001$) in both groups, but the ΔT0-T20 was 4.12 minutes in the MD group and 2.64 minutes in the control group. This difference has to be considered clinically significant. MD showed a continuous VAS total and mean score improvement along all time-intervals, resulting superior to saline at T10-T20 ($p<0.001$ vs $p<0.05$ in saline). Nasal obstruction was back 30 days after the end of treatment in both the groups, but in saline patients only it was judged as moderate/severe. The symptom was present in only 3 patients from the MD group, and reported to be in a mild form.

CONCLUSION. The obtained results show that only the MD has added to the mechanical action of removal of secretions a specific decongestant and antiseptic effect lasting longer after the end of the treatment. In view of its natural decongestant activity and of its hydrating effects, SILSOS® hyper could help to fluidize thick mucus, improve respiration and promote resolution of symptoms, preventing pathogens adhesion to nasal mucosa

KEYWORDS: nasal obstruction, VAS, SNOT-22, rhinopathy, SILSOS® hyper

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INTRODUCTION

The complaint of nasal obstruction is a frequent and complex clinical problem because of mucosal inflammation, decreased nasal patency, structural and psychological factors. Congestion, which may be best described as a feeling of blockage, fullness or restricted airflow, is the primary symptom of common upper respiratory tract disorders, including common cold and acute and chronic rhinosinusitis with/without nasal polyposis.

Rhinosinusitis is defined as a mucosal inflammatory status of the functional unit composed of nasal cavities and paranasal sinuses; it is characterized by two or more symptoms, one of which should be either nasal obstruction/congestion/blockage, or nasal discharge (anterior/posterior nasal drip) ± facial pain/pressure or ± reduction or loss of smell[1-3]. Generally, the subjective sensation of nasal obstruction and rhinomanometric nasal resistance or nasal peak flow show a good intra-individual correlation in a number of studies in healthy volunteers, in patients with structural abnormalities as well as in hyper-reactive or infective rhinitis[4,5], although some reports did not confirm these data[6].

In patients affected by sinonasal diseases of different aetiology, transudation is reported to increase and thicken the periciliary layer and impair the mucociliary clearance (MCC) and/or the mucociliary transport time (MCTt). In the upper airways, MCC and MCTt are preventative mechanisms against the deposition of inhaled, potentially pro-inflammatory particulate matter as well as the harboring of infections, particularly at the level of paranasal sinuses[7-10]. Besides the discomfort given by the swelling of nasal mucosa, rhinosinusitis is diagnosed when nasal obstruction or serous/purulent, anterior/posterior rhinorrhea does occur. The stasis of thickened secretions allows microorganisms to settle and proliferate on sinonasal mucosa, leading to an inflammatory mucosal reaction, further exacerbating sinonasal symptoms and facilitating onset and/or recurrence of infections. Therefore, facilitating solubilisation and discharge of thickened secretions and thereby counter-fighting microbial colonization of nasal mucosa constitute a mainstay of symptom resolution and functional recovery. To this end, International Treatment Guidelines indicate isotonic and hypertonic saline nasal wash/irrigation as a safe and effective intervention, alone or in adjunct to medical therapy, to promote MCC/MCTt recovery, to improve moisturization of nasal epithelia and to facilitate the removal of microorganisms and encrusted material[11,12].

In patients with acute URTIs (Upper Respiratory Tract Infections) saline nasal irrigation is associated with less time off work and with a trend towards less antibiotic usage[13]. In chronic rhinosinusitis saline is beneficial in the treatment of the symptoms when used as the sole modality or as a treatment adjunct[11]. Hypertonic saline solutions are also reported to reduce nasal mucosal edema[14] and to improve mucociliary clearance[15]. In clinical practice and in several nasal affections, e.g. seasonal nasal discomfort and in the post-surgery period, nasal saline solutions are always recommended for the cleansing of nasal cavities. Overall, saline solutions contribute to efficiently relieve nasal symptoms with a good safety profile, despite reports of nasal burning and irritation upon saline exposure[11].

A new Medical Device (MD, SILSOS® hyper, CM&D Pharma Limited) composed of the synergistic association of two parent molecules: the patented silver salt Silver Sucrose Octasulfate (IASOS® ; US71833[15], EP1458733) and Potassium Sucrose Octasulfate (KSOS) has been recently developed to facilitate mucosal decongestion and hydration, and elimination of thick secretions, thereby halting inflammation and counter-fighting the harboring of mucosal infections, according to a non-pharmacological mechanism of action. The patented association of IASOS® and KSOS (US61/715226) is expected to simultaneously exert an antimicrobial protection and a repairing effect on nasal mucosa, due to the combined antimicrobial property of IASOS® and the carbohydrate-based microbial antiadhesion of KSOS, further reinforced by its trophic effect through Fibroblast Growth Factor (FGF) pathway activation[16,17]. The whole formulation is mildly hypertonic with an anti-edema activity, while locally establishes a protective shield against microbial adhesion. We therefore designed a randomized, double-blind, active comparator (isotonic, nasal saline solution) controlled, parallel study to evaluate the safety and the efficacy of SILSOS® hyper in patients suffering from obstructive rhinopathy of different aetiology and with nasal obstruction/congestion of moderate severity, lasting since at least 10 days, for whom a bacterial superinfection could be suspected.

MATERIAL AND METHODS

Study design and eligibility

A randomized, double-blind, active comparator controlled, parallel study was performed. Eligible participants were adult male and female outpatients aged 18-70, with or without rhinosinusitis, suffering from obstructive rhinopathy of various aetiologies and with symptoms persistent since at least 10 days in advance of recruitment. At baseline (T0), eligible participants were categorized for disease severity on the 10-cm visual analogue scale (VAS) validated for use in patients with rhinosinusitis, and rated as Moderate (VAS> 3-7; EPOS and BSACI guidelines[1,3,4]).

Inclusion criteria further required the moderate score to be achieved as the result of: **a)** a VAS > 5 for two of the primary symptoms: nasal congestion, nasal obstruction and rhinorrea, or **b)** a VAS > 5 for one of the primary symptoms above + a moderate score for at least one of the secondary symptoms: facial pain/pressure, reduction or loss of smell. Due to the fact that a VAS > 5 does impact on health related quality of life (HRQoL[18]), the validated 22-items Sino-Nasal Outcome Tests (SNOT-22[19]), ranging from 0 (absence of symptoms) to 5 (the highest severity degree) was also performed.

Exclusion criteria were pregnancy, persistent/intermittent allergic rhinitis, cystic fibrosis, diagnosis of nasal polyps (Lund/McKay II-III degree); participation in other clinical trials within 3 months from enrolment; treatment with local and/or systemic corticosteroid, antibiotic, decongestants and nasal saline washes within one week from enrolment.

50 subjects met the inclusion criteria. After receiving detailed information about the trial aim and related experimental procedures, all participants signed their Informed Consent in compliance with the Declaration of Helsinki and current Good Clinical Practice (cGCP). The study protocol was approved by the Ethics Committee of the University Hospital "Le Scotte", Siena (Nr 93/2011, November 22, 2011).

Study procedures

At baseline (T0), ten days (T10) and twenty days (T20) after saline or SILSOS® treatment, study participants were evaluated subjectively with VAS and SNOT-22, and objectively with left and right, and total Nasal Airflow Resistance (NAR) by Active Anterior Rhinomanometry (AAR, Expressed in Pascal/ml/second (Pa/ml/s); total NAR was calculated as follows: $NAR_{total} = NAR_{left} \times NAR_{right} / NAR_{left} + NAR_{right}$[20].

MCC and MCTt were determined by means of the charcoal+3% saccharine test. Whereas the insoluble charcoal powder traces and measures the transport of foreign bodies like bacteria or dust particles entrapped into the outer mucus layer, the soluble saccharine traces and measures the clearance (i.e. the dilution and drainage) of solutes into the inner mucus layer. Moreover, the charcoal powder is easily detectable on the red pharyngeal wall thereby providing an objective measurement of the transport time. The patient's perception of the sweet saccharine taste represents a subjective parameter[21]. MCC/MCTt is reported to take more than 30 minutes in pathological conditions; MCTt normal values are 13 (+/-2) minutes in adults and 8 (+/-3) in children; MCC normal values are 17 (+/-5) minutes in adults and 11 (+/-6) in children[21].

All patients were followed-up 30 days after the end of the treatment by mean of a phone interview aimed to evaluate the long term effectiveness of the treatment.

Study interventions

According to a computer-generated randomization list, enrolled subjects were 1:1 randomized (in blocks of ten) to receive either a nasal dispenser of isotonic saline solution (saline; 0.9% sodium chloride) or the MD (SILSOS® hyper, containing 25 ppm silver ions and 1.5% KSOS). Osmolarity and pH were: 294 mOsm/kg and 6.76, 397 mOsm/kg and 6.71 in saline and MD, respectively. Test solutions were packed in perfectly identical nasal dispensers, with a metered spray volume of 130µl. Only one dispenser/patient was needed. Treatment consisted of 2 sprays per nostril, two times a day for 20 days. As a matter of fact, 1.04 ml (or g) had to be daily inhaled, leading to 20.8 ml inhaled treatment volume over the 20 days study period. To assess compliance to test solutions, the dispenser weight at T0 (DW, g) and the residual dispenser weight (RDW, g) at T20 were recorded.

Study endpoints

The primary endpoint was the assessment of MD superiority versus saline on MCC and MCTt. Secondary endpoint was the achievement - within and between study arms - of a reduction in: Total primary symptoms, Total primary and secondary symptoms, and Mean VAS scores as well as SNOT-22 in the T0-T10 and T10-T20 interval time and in the overall treatment period (T0-T20).

Sample size and statistical analysis

This study was 90% powered at an α error of 0.025 to detect a 5 (±5 SD) minutes improvement in MCC/MCTt, following 20 days of treatment by the MD. In a randomized, parallel 1:1 design (22 placebo and 22 SILSOS®, MD), 44 randomised subjects were needed to match the primary endpoint. Assuming a drop-out rate of 10%, the total sample size was 50 subjects. The statistical plan was designed to accommodate Intent To Treat (ITT) and Per Protocol Participants (PPP) analysis. ANOVA was performed on continuous variables and categorical variables. χ2-test or Kruskal-Wallis was applied as appropriate for significance between treatment groups (Saline vs MD). Significance of intra- and inter-arm changes in secondary endpoints at different time intervals (T0-T10, T10-T20, T0-T20) was assessed in the Paired-Sample Wilcoxon Signed Rank Test. Proportion of participants with adverse effects attributed to treatment was also computed. Tests were performed using the R system.

RESULTS

All N=50 subjects enrolled in the study in the timeframe February-May 2012, completed the study. Demographics and clinical history of study partici-

pants at baseline (T0) are reported in Table1. Although well balanced in demographics, we found a clinically lower percentage of rhinosinusitis than expected.

AAR analysis (Table 2) showed that at baseline and similarly in both treatment groups, total NAR was more than double the healthy (0.25 Pa/ml/s reported) value[20]. When compared to the saline group, MD group trended to a higher total NAR at T0. Whereas saline resulted ineffective on improving inspiratory and expiratory flow at any study time point, MD patients progressively and significantly ($p<0.05$, Kruskal-Wallis test) ameliorated in expiratory flow, at T0-T10 as well over the whole study period (T0-T20).

Tables 3 and 4 report MCTt and MCC values at baseline and after ten (T10) and twenty (T20) days of treatment. Neither study groups presented with impaired sinonasal MCTt values at T0 while MCC times were at the upper limits of the normal range. No improvement in MCTt was observed over the 20 days study period, or at T0-T10 and T10-T20 time points, irrespective of PROMs scores as per VAS (Table5) and SNOT-22 (Table 6). As the MCC is concerned, the

Table 1
Baseline characteristics of study group patients. Data are represented as follows: median (I quartile; III quartile) for continuous variables and Percentage value (absolute frequency).

Population	Saline solution N=25	MD ear N=25
Demographics		
Age	35 (25; 45)	30 (25; 48)
Male	36% (9)	36% (9)
Female	64% (16)	64% (16)
Clinical history		
Rhinosinusitis	36% (9)	36% (9)
Recurrent Rhinosinusitis	78% (7)	22% (2)

Table 2
AAR: Total nasal resistance (Pa/ml/s) in study groups at different time points

	SALINE Total Resistance		MD Total Resistance (Pa/ml/ s)	
Time	Inspiratory flow	Expiratory flow	Inspiratory flow	Expiratory flow
T = 0	0.533 ± 0.439	0.542 ± 0.435	0.660 ± 0.601	0.662 ± 0.579
T = 10	0.437 ± 0.336	0.392 ± 0.285	0.510 ± 0.427	0.470 ± 0.327*
T = 20	0.386 ± 0.207	0.375 ± 0.212	0.420 ± 0.218	0.382 ± 0.205*

*p<0.05 versus T0, Kruskal-Wallis test

Table 3
MCTt at T0, T10 and T20. Data express the median (I; III quartile) and (mean + SD).

MCTt	Saline N=25		MD N=25		P
T0	13.0 (12.0; 14.0)	(13.0±1.3)	13.0 (12.0; 14.0	(13.0±1.1)	0.61
T10	13.0 (13.0; 13.0)	(12.88±0.78)	13.0 (12.0; 13.0)	(12.64±0.81)	0.22
T20	13.0 (12.0; 13.0)	(12.64±0.86)	13.0 (12.0; 13.0)	(12.72±0.84)	0.8

Table 4
MCC at T0, T10 and T20 and differences in time (ΔTime). Data express the mean ± SD and standard error (SE)

	SALINE N=25	MD N=25
T0	21.52 ± 4.593 (0.877)	20.20 ± 4.387 (0.877)
T10	19.68 ± 4.498 (0.899)	17.96 ± 4.228 (0.845)
T20	18.88 ± 5.480 (1.096)	16.08 ± 4.242 (0.848)
ΔTime	2.64 ± 3.147 (0.623)	4.12 ± 4.003 (0.801)

Table 5
VAS Total and Mean Score (mean±SD) at different time points in the two study groups

	Primary Symptoms VAS Total Score (N=25/group)		Primary + Secondary Symptoms VAS Total Score (N=25/group)		Total score/n Symptoms VAS Mean Score (N=25/group)	
Treatment	SALINE	MD	SALINE	MD	SALINE	MD
T = 0	11.2 ± 3.7	11.5 ± 3.4	15.5 ± 4.5	15.6 ± 3.7	5.6 ± 1.7	5.7 ± 1.5
T = 10	8.6 ± 2.7^{A}	9.6 ± 3.1^{A}	12.4 ± 4.0^{A}	12.8 ± 3.5^{A*}	4.7 ± 1.3^{A}	4.9 ± 1.3^{A}
T = 20	7.1 ± 3.2^{B*}	7.6 ± 2.8$^{B*, C}$	10.5 ± 4.1^{B*}	10.5 ± 4.0$^{A*, C*}$	4.0 ± 1.5^{B*}	4 ± 1.3$^{B*, C}$

Interval treatment time: A=T0-T10; B=T0-T20; C=T10-T20.
Significance: A, B, C: $p < 0.05$ within treatment group; A*, B*,C*: $p<0.001$ within treatment group.

Table 6
Effect of the two treatments on the SNOT-22 Scores

ITEMS	Saline			MD		
	T0	**T10**	**T20**	**T0**	**T10**	**T20**
Need to blow the nose	2.00 ± 1.3	1.90 ± 1.1	1.90 ± 1.2	2.12 ± 1.0	2.28 ± 1.0	2.04 ± 1.0
Sneezing	1.48 ± 1,3	1.00 ± 1.1	0.68 ± 1.1*	1.40 ± 1.2	1.08 ± 0.9	0.88 ± 0.9
Runny nose	1.30 ± 1,4	1.60 ± 1.3	1.70 ± 1.2	2.00 ± 1.6	2.00 ± 1.5	2.00 ± 1.3
Cough	0.76 ± 1,3	0.52 ± 1.0	0.52 ± 1.0	0.76 ± 1.0	0.52 ± 0.8	0.44 ± 0.9
Posterior nasal discharge	2.36 ± 1,4	1.68 ± 1.4	1.54 ± 1.1*	1.68 ± 1.5	1.16 ± 1.1	0.60 ± 0.8*
Thick nasal discharge	1.92 ± 1,5	1.32 ± 1.3	0.92 ± 1.1*	1.28 ± 1.1	0.72 ± 0.7	0.56 ± 0.8*
Ear fullness	1.96 ± 1,2	1.76 ± 1.2	1.28 ± 0.9*	1.40 ± 1.0	1.20 ± 0.7	0.92 ± 0.5*
Dizziness	----------	----------	----------	----------	----------	----------
Ear pain	0.24 ± 0.7	0.12 ± 0.4	0.20 ± 0.6	0.12 ± 0.4	0.08 ± 0.3	0.00 ± 0.0
Facial pain/pressure	1.52 ± 1.7	1.08 ± 1.5	0.96 ± 1.3	1.12 ± 1.5	0.84 ± 1.3	0.76 ± 1.2
Difficulty falling asleep	1.80 ± 1.6	1.70 ± 1.5	1.50 ± 1.2	1.80 ± 1.5	1.60 ± 1.3	1.60 ± 1.3
Waking up at night	2.00 ± 1.4	1.80 ± 1.3	1.60 ± 1.1	1.90 ± 1.3	1.40 ± 1.2	1.40 ± 1.2
Lack of a good night sleep	2.20 ± 1.4	2.00 ± 1.3	1.70 ± 1.0	2.10 ± 1.4	1.60 ± 1.3	1.60 ± 1.2
Waking up tired	2.32 ± 1.4	2.16 ± 1.2	1.76 ± 1.0	2.00 ± 1.4	1.80 ± 1.1	1.80 ± 1.2
Fatigue	2.00 ± 1.6	1.60 ± 1.4	1.50 ± 1.1	1.90 ± 1.4	1.70 ± 1.2	1.40 ± 1.3
Reduced productivity	0.96 ± 1.2	0.64 ± 0.9	0.32 ± 0.7*	0.80 ± 1.1	0.64 ± 1.1	0.16± 0.5$^{**°}$
Reduced concentration	0.96 ± 1.2	0.72 ± 1.0	0.40 ± 0.8*	1.20 ± 1.0	0.64 ± 1.0*	0.40 ± 0.9**
Frustrated/restless/irritable	0.60 ± 1.2	0.32 ± 0.9	0.24 ± 0.7	0.60 ± 1.0	0.36 ± 0.9	0.40 ± 1.1
Sad	0.33 ± 1.0	0.20 ± 0.8	0.16 ± 0.6	0.04 ± 0.2	0.04 ± 0.2	0.12 ± 0.6
Embarrassed	0.40 ± 1.1	0.24 ± 0.8	0.16 ± 0.6	0.04 ± 0.2	0.08 ± 0.3	0.12 ± 0.6
Sense of smell/taste	1.25 ± 1.4	0.80 ± 1.2	0.68 ± 1.2	1.48 ±1.6	0.88 ± 1.4	0.68 ± 1.2
Nasal obstruction/congestion	4.00 ± 1.1	3.10 ± 1.1**	2.80 ± 1.2**	4.64 ± 0.5	3.72± 0.8**	2.96± 0.9$^{** Δ}$
TOTAL SCORE	33.0 ± 12.0	26.0 ± 10.0*	22.0 ± 11.0**	30.0 ± 9.7	24.2 ± 8.4*	20.8 ± 8.7**

T20 versus T0 : $^{*}p<0,05$ $^{**}p< 0.001$; T20 versus T10 : $^{°}p<0,05$, $^{Δ}p< 0.005$ (Wilcoxon Test)

mean values significantly improved at T20 ($p<0.0001$, ANOVA) in both groups, but the ΔT0-T20 was 4.12 minutes in the MD group and 2.64 minutes in the control group. These differences have to be considered clinically significant.

Table 5 reports the VAS total score (mean±SD) for primary, primary and secondary symptoms, and the VAS mean score (mean±SD), defined by the formula: Total symptoms score/n symptoms, and expressing the severity of the experienced symptoms. In agreement with protocol inclusion criteria, patients entered the study with similar VAS total score for primary, and primary and secondary symptoms. The VAS mean score also resulted similar, although MD participants presented with a higher degree of severity for anterior catarrhal rhinorrea (data not shown). On the overall treatment period (T0-T20), saline and MD similarly improved VAS total score for primary, primary and secondary symptoms, and VAS mean score ($p<0.05$ vs T0). MD showed a continuous VAS total and mean score improvement along all time-intervals, resulting superior to saline at T10-T20 ($p<0.001$ vs $p<0.05$ in saline). Overall, the SILSOS® hyper MD demonstrated to be as effective as isotonic saline on MCTt, but showed more evident improvement of MCC times and better scores in primary, primary and secondary symptoms, and their severity degree at T10-T20.

Saline and MD effect on nasal obstruction/congestion and nasal discharge, being the symptoms of relevance in the clinical diagnosis of rhinosinusitis, were also considered in the small, good balanced subgroup of rhinosinusitis patients. Results are summarized in Figure 1.

45/50 patients in study group participated in the follow-up interview at 30 days after treatment withdrawal. 5/25 patients of the saline group reported the presence of subjective nasal obstruction, which was of moderate or serious intensity for 3/5 patients. In the MD group only 3/25 patients reported the presence of subjective nasal obstruction, which was graded as a mild form.

DISCUSSIONS

In our study population, nasal obstruction was the most relevant patients' complaint as well as a major inclusion criteria to enrolment. After treatment, the more striking effect observed in both study groups was the significantly decreased scoring for nasal obstruction/congestion on the overall treatment period. The symptom relief resulted to depend upon amelioration of posterior nasal discharge, thick discharge and ear fullness. These parameters suggest an effective fluidification of sinonasal secretions, supporting the recovery on HRQoL. Although the two treatments resulted similarly effective on the relief of primary symptoms, SILSOS® hyper showed superiority against saline on items such as ear fullness and ear pain, and a trend to a better performance on facial pain/pressure as well. On all these items included in the VAS>5 scoring for patients inclusion into the study, saline resulted ineffective.

Although subjective assessment of nasal obstruction by PROMs is a well-validated criterion, if little correlation were found between a patient-based symptom severity-scoring systems and an objective respiratory parameter, the impact of symptom amelioration could be overestimated. In our patients, a good matching of ameliorated PROMs and total nasal resistance was observed at T20 in both study groups, indicating an improved respiration. Noteworthy, SILSOS® hyper resulted superior to saline on the overall functional recovery in nasal patency.

Rhinomanometry has been reported to correlate with subjective symptom scoring with and without decongestion[22]. Generally the subjective sensation of nasal obstruction and rhinomanometric flow evalua-

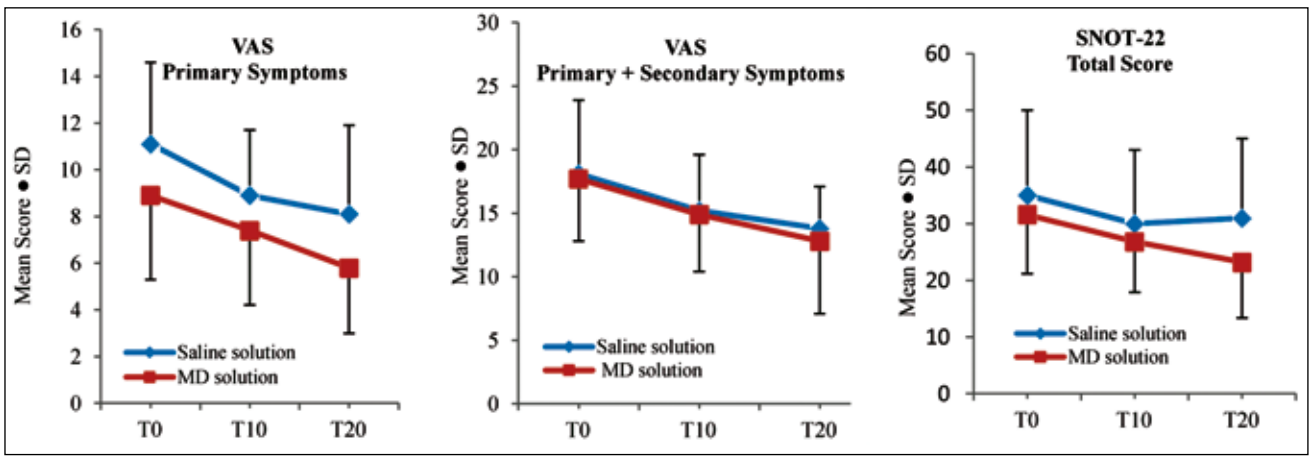

Figure 1 Symptoms improvement in Rhinosinusitis patients at T20

tions show a good intra-individual correlation in a number of studies considering normal controls, patients with structural abnormalities, hyper-reactivity or infective rhinitis[23-28]. Although some reports did not confirm these data[29] or showed weak correlations between PROMs and rhinomanometry[30-32], the absence of correlation does not necessarily suggest that either subjective or objective scores are invalid, because the two approaches measure different aspects of the disease process. Therefore, both assessments are useful adjuncts in outcome measurement. Subjective nasal obstruction correlates better with objective functional measurements of nasal airflow resistance (rhinomanometry, peak flow) than with measurements of nasal cavity width, such as acoustic rhinometry[27,33]. The measurement of nasal airway resistance by assessing nasal flow at a constant pressure can be useful in confirming that improvement in nasal congestion is the result of reduction of inflammation in the middle meatus rather than mechanical obstruction.

So as the primary endpoint of our study is concerned, there is a limitation in that on inclusion, patients had normal MCTt values and MCC times were at the upper limits of the normal range. Hence, no large improvements could be expected from one to two week course of treatment. Considering these baseline values, the observed improvement in MCC can indeed be interpreted as clinically convincing. The greater effectiveness of the MD on the MCC times could depend on its hyper osmolarity. As previously reported[15], hypertonic solutions are reported to be more effective than isotonic solution since the drainage of the solutes into the inner "sol" layer can benefit of the dilution induced by the osmotic effect. MCTt is expression of the equilibrium between both the inner "sol" layer and the outer "gel" layer and therefore, it needs prolonged or repeated treatments before a change could be appreciated.

In our study, an interesting suggestion comes from subjectively reported recurrences at follow-up. Nasal obstruction was back 30 days after the end of the treatment in both groups, but in saline patients only it was judged as moderate/severe. The symptom was present in only 3 patients from the MD group, and reported to be in a mild form. Therefore, it seems that only the MD has added to the mechanical action of removal of secretions a specific decongestant and antiseptic effect lasting longer after the end of treatment.

CONCLUSIONS

In conclusion, in view of its natural decongestant activity and of its hydrating effects, SILSOS® hyper could help to fluidize thick mucus, improve respiration and promote resolution of symptoms, maybe preventing pathogens adhesion to nasal mucosa. To this end, a dedicated study would be of relevance. Both saline and SILSOS® hyper were optimally tolerated by patients since no adverse effect or complaints was recorded during the study and compliance was 78% in both groups.

Worth noting that SILSOS® hyper does not contain any Sodium Chloride in its formulation, so that local discomfort such as burning and bleeding, sometime reported for nasal physiological solutions, are excluded. The new MD seems to constitute a safe alternative to current nasal salty preparations, alone or in adjunct to the medical therapy, with the advantage of a superior symptom relief because of the improved ear fullness and ear pain, on top of all the other tested HRQoL assessments.

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Running title

Relief of nasal symptoms with SILSOS® Hyper

Conflict of Interest

MC Comelli and G Calderini were employers and Scientific Advisers at CM&D Pharma, respectively, at the time of manuscript drafting and submission.

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