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Research Article

Safety and Efficacy Assessment of Stérimar Stop and Protect Cold for Adults and Stérimar Blocked Nose in Common Cold: A Randomized, Double-blind, Controlled Parallel-group, Clinical Study

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Abstract

Background: Current treatment options for common cold focus on symptomatic relief. Nasal irrigation is a safe, inexpensive and effective adjunct treatment to reduce common cold-associated nasal congestion; it also improves quality of life and decreases medication use.

Purpose: The objective of this work was to investigate safety and efficacy of a novel microfiltered hypertonic seawater solution enriched with hyaluronic acids, eucalyptus oil and copper salts (SSPCA) on relieving common cold symptoms in comparison to a hypertonic seawater solution enriched with copper salts only (SBN).

Methods: In total, 102 common cold patients were randomized to use SSPCA (n = 51) or SBN (n = 51) until their common cold episode was resolved (maximum 14 days). Illness severity evaluated by means of the validated 21-item Wisconsin Upper Respiratory Symptom Survey (WURSS-21) was the primary endpoint. Illness duration, use of rescue medication, patient satisfaction and acceptability were secondary endpoints measured through patient diaries. In addition, nasal presence of 24 airway pathogens was screened via RT-PCR before and after treatment.

Results: Based on subjective patient diaries, SSPCA was as effective as SBN in reducing overall illness/symptom severity, improving quality of life and satisfying patient expectations. SSPCA had a faster onset of action than SBN in nasal decongestion ($p = 0.0056$), symptom and breathing relief ($p = 0.0028$ and $p = 0.0128$, respectively), stopping cold symptoms ($p = 0.0002$), and improving nasal well-being ($p = 0.0279$). Amount of airway pathogens - including rhino- and adenoviruses - was significantly lower after the treatment compared to pre-treatment, with no difference between groups. No adverse events were reported.

Conclusion: Both SSPCA and SBN appear to be safe and effective solutions that enable symptomatic relief and decrease the presence of nasal viruses in common cold patients. However, SSPCA had a faster onset of action compared to SBN in nasal decongestion and breathing relief, improving common cold symptoms and nasal well-being.

Trial registration: ISRCTN, ISRCTN14067635 (retrospectively registered). Available at: https://www.isrctn.com/ISRCTN14067635

Keywords: Nasal Irrigation; Common Cold; Hypertonic Solutions; Seawater; Hyaluronic Acid; Copper

Abbreviations

COPD: Chronic Obstructive Pulmonary Disease; CRO: Clinical Research Organization; GCP: Good Clinical Practices; ITT: Intention-to-treat; NaCl: Sodium Chloride; OTC: Over-the-counter Drug; PP: Per-protocol; qRT-PCR: Quantitative Reverse Transcription Polymerase Chain Reaction; SBN: Stérimar Blocked Nose; SD: Standard Deviation; SEM: Standard Error Mean; SNPC: Stérimar Nose Prone to Cold; SSPCA: Stérimar Stop and Protect Cold for Adults; WURSS-21: 21-item Wisconsin Upper Respiratory Symptom Survey

Introduction

Common cold is the most frequent illness in the world and is one of the leading causes of doctor visits and missed days from school and work [1]. A recent survey revealed that common cold is responsible for a mean 26.4% decrease in productivity and 1-2 days off work or school in 44.5% of the respondents [2]. The principal causing factor for common cold is viral infection. More than 200 viruses are known to cause common cold, with rhinoviruses accounting for the majority of cases [3]. In addition, the evolution of new strains represents a challenge against the development of asthma [4]. Children and adults are estimated to suffer from up to 5 and 3 cold episodes per year, respectively [5].

Current treatment options for common cold are symptomatic and relief-oriented while the body overcomes the infection [6]. These options include getting enough rest, drinking plenty of water and eliminating congestion caused by mucosal edema and secretions that accumulate in the nasal cavity. For the latter, use of nasal irrigation is a safe, simple, inexpensive and effective approach which helps eliminate thick secretions, remove excess viruses from the upper respiratory tract and inhibit their replication [7,8]. Nasal irrigation with isotonic and/or hypertonic saline solutions is widely recommended by physicians for upper respiratory conditions [9]. It has also been shown to decrease the use of medication, e.g. antibiotics used to treat consecutive bacterial superinfections, which in turn prevents development of antibiotic resistance [10].

Saline nasal irrigation can be performed by using isotonic (0.9% NaCl) [11] or hypertonic (>0.9% NaCl) solutions [12,13] both in adults and children. However, hypertonic solutions are more effective in cleaning the congested nasal cavities as they induce osmosis, draw excess water from the surrounding swollen mucosa and contribute to the elimination of thick, obstructive mucus [14]. In chronic rhinosinusitis patients, a hypertonic seawater solution has been shown to be better than an isotonic seawater solution in alleviating symptoms such as nasal congestion, rhinorrhea, cough and headache [15]. Pressurized jets of saline have been shown to be more effective than drops [8].

Stérimar Stop and Protect Cold for Adults (SSPCA) is a novel, microfiltered hypertonic seawater solution (2.3% NaCl) enriched with hyaluronic acids of different molecular weights, Caprylyl/Capryl glucoside, eucalyptus oil, and copper and manganese salts. The aim of this randomized, double blind study was to examine and confirm the safety and the efficacy of SSPCA for relieving the symptomatology of common cold in comparison to a benchmark product, Stérimar Blocked Nose (SBN), a hypertonic seawater solution enriched with copper and manganese salts, previously shown to be effective in eliminating chronic rhinosinusitis-associated symptoms [15]. This clinical study was performed in order to assess and compare the efficacy and safety profile of the two solutions (SBN and SSPCA).

Materials and Methods

Study design and population

One hundred and two patients with acute upper respiratory tract infection (common cold) were enrolled in this randomized, double-blind, parallel group clinical trial. Subjects were screened and asked to schedule a visit to the centers (Centre of Clinical Pharmacology for the Experimentation of Pharmaceuticals, University Hospital of Pisa, Pisa, Italy or ENT Department of University Hospital Polyclinic Vittorio Emanuele, Catania, Italy) 24-48 hours after common cold onset, between April 2016 and April 2018. The trial was retrospectively registered with ISRCTN, trial registration number ISRCTN14067635.

Randomization and blinding

A simple randomization technique based on a single sequence of random assignments has been used. A random list of numbers were generated by SAS software, and subjects were assigned to a number according to their order of inclusion in the study. Subjects meeting eligible criteria were randomized to one of the two study groups at 1:1 ratio. Since no stratification was requiered for the study, no blocks of randomization have been used. The blinded randomization list was distributed to clinical sites together with

product labeling and sealed code breaks. Clinical sites, following the sequential blinded randomization list, assigned the random code kit to the corresponding subIDs generated upon enrollment of subjects. SubID logs and randomization logs were filled by the investigators and were archived in the study investigator trial center file. Randomization list was generated by CRO biostatistician. CRO provided the blinded randomization list to the clinical sites and investigators who were resposible for the participant enrollment. All participants in the study (patients, investigators, nurses, personnel involved in monitoring study, and data entry personnel) were blinded to the identity of the study treatment and had no access to the patient codes.

Eligibility criteria

- **Inclusion criteria:** Subjects between 18 and 60 years of age with common cold symptoms starting at 24 - 48 hours before enrollment; Jackson score [16] between 2 - 9 (both inclusive) and with at least one of the first four major symptoms (nasal discharge, congested nose, sneezing, sore throat) at the enrollment time.
- **Exclusion criteria:** Patients with symptoms starting > 48 hours before enrollment; oral temperature > 38.9°C; streptococcal antigen positive results; signs of lower respiratory tract disease; having current or history of allergic (seasonal or perennial) rhinitis, asthma, bronchitis, recent sinusitis, otitis or pharyngitis; reporting cough, wheezing, itching of the nose or eyes, shortness of breath at the time of enrollment; history of immune system disorders or a clinically significant cardiovascular, endocrine, neurological, respiratory, or any other current disease (such as chronic respiratory, lung disease or COPD); severe nasal septum deviation or other current condition that can cause nasal obstruction such as nasal polyps or nasal/sinus surgery in the past, able to influence symptoms scores; pregnancy; use of OTC or prescribed medication (other than contraception) able to influence symptoms scores at the time of enrollment such as saline nose drops or nasal sprays or pumps other than the study products, antibiotics, antivirals, nasal or systemic steroids, nonsteroidal anti-inflammatory drugs and analgesics (except acetaminophen), intranasal medicines, decongestants, antihistamines, combination cold formulas, Echinacea, supplements containing ≥ 10 mg zinc or ≥ 100 mg vitamin C; hypersensitivity or allergy to any component of the study medication or to acetaminophen; smoking during the past 12 months; history of alcohol or drug abuse; participation to any investigational drug trial within 4 weeks before screening.

Sample size calculation

Considering the non-inferiority design between the two formulas, if there were truly no difference between the two formulas (SSPCA and SBN), 92 patients are required to be 90% sure that the upper limit of a one-sided 97.5% confidence interval (or equivalently a 95% two-sided confidence interval) excludes a difference in favour of the reference product of more than 28. A total of 102 patients to account for a 10% drop out rate will be required. Calculation was based on the following formula: $n = [(Z_{1-\alpha}+Z_{1-ß})^2 x 2\sigma^2]/(\mu c-\mu s-\delta)^2$ ($Z_{1-\alpha}$ and $Z_{1-ß}$: the cumulative distribution functions of deviate standardized normal; α - type I error or false positive: the probability that an experimental therapy is thought to be inferior to a standard therapy, when no difference actually exists; ß - type II error or false negative: the probability that the experimental therapy is concluded to be no better than the standard when in fact there is a difference; σ^2: is the pooled variance estimate for the WURSS-21 scale difference in mean; μs and μc: the population WURSS-21 scale means for SSPCA and SBN groups, respectively; δ: the non-inferiority limit, defined as a difference in mean from the competitive treatment).

Treatments and methodology

Initial visit (V0)- Screening and randomization

The details of visits (initial, V0; final, V1) are given in figure 1.

At V0, products were supplied and instruction were given: two pulverizations/nostril when needed up to 6 times a day, starting from V0 until symptoms were resolved and patients answered "No" to the question "Do you feel you still have a cold?" for two days in a row, or for a maximum of 14 days from study initiation. Patients were asked to avoid medication. Acetaminophen was allowed as rescue medication (maximum dose of 500 mg for every 4-6 hours). Patients were requested to fill the diary with product use, symptomatology, concomitant medication, rescue medication and adverse events. Starting from V0 patients were requested to com-

plete the 21-item Wisconsin Upper Respiratory Symptom Survey (WURSS-21) questionnaire for symptomatology and quality of life, daily until the end of the study. WURSS-21 is an evaluative illness-specific quality of life instrument, designed to assess the negative impact of acute upper respiratory infection (common cold). V1 was scheduled as soon as possible within the first 2 days from the end of the common cold symptoms, but not later than 14 + 2 days from the beginning of the study. Unused/empty product bottles and diaries were collected to evaluate treatment adherence based on final weight of the bottles and symptom resolution, respectively.

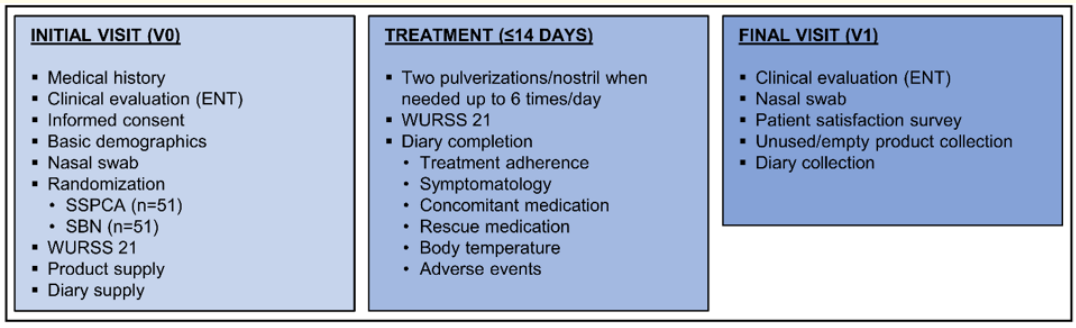

Figure 1: Trial flowchart. Details of evaluations at each visit and during treatment period. SSPCA: Stérimar Stop and Protect Cold for Adults; SBN: Stérimar Blocked Nose; WURSS: Wisconsin Upper Respiratory Symptom Survey.
172 x 52 mm (600 x 600 DPI).

Endpoints

Primary endpoint was illness severity (evaluated by means of the WURSS-21 score) analysed on intention-to-treat (ITT) and per-protocol (PP) populations. Secondary endpoints were (i) illness duration (evaluated by days elapsed from enrollment until last time answering "Yes" to the question "Do you feel you still have a cold?"), (ii) use of rescue medication (evaluated by means of diary registers), (iii) patient satisfaction (evaluated by means of the score recorded using a 10-point Likert scale), (iv) patient acceptability (evaluated by means of the score recorded using a 10-point Likert scale) and (v) willingness to use the product in the future (evaluated by means of the score recorded using a 4-point scale), analysed on ITT and PP populations. The safety was evaluated by means of the assessment of all adverse or serious adverse events reported during the study.

Additional outcome variables

Additional statistical analyses were performed on data from the first 7 days after onset of symptoms, collected from patient diaries (ITT population), considering that this is the average duration of a common cold episode [17] and that the majority of the patients completed the study within the first 7 days of treatment. Average number of patients was calculated as follows: sum of number of patients each day divided by 7 (number of days). Patients were asked to use a stopwatch for recording the time elapsed between product application and observed outcomes as previously described [18].

Nasal swab evaluations

During V0 and V1 a nasal swab was collected using Virocult™ (Sigma, St. Louis, Missouri, United States) and sent for laboratory analyses, to screen for the presence of the following pathogens: Influenza A and B viruses, Respiratory Syncytial viruses A and B, FluA-H1, Adenovirus, Enterovirus, Parainfluenza viruses 1-4, Metapneumovirus, Bocavirus, Rhinovirus, Coronavirus NL63, Coronavirus 229E, Coronavirus OC43, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumoniae*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Bordetella pertussis*, and *Bordetella parapertussis*. For each virus type, the amount of viral particles were normalized to the amounts at Visit 0. The levels of virus at this visit were considered as 1.

Statistical analysis

Wilcoxon Rank Sum Tests were performed for both primary and secondary endpoints. For sub-group analyses, parametric t-tests were performed for data with normal distribution and Wilcoxon Rank Sum Tests were performed for data without normal distribution.

Ethical considerations

This study was conducted according to GCP as defined in the ICH E6 Guideline for Good Clinical Practice (10 June 1996) in agreement with the latest locally applicable revision of the Declaration of Helsinki and other local regulations. The Ethics Committee of Azienda Ospedaliero-Universitaria Pisana approved the final version of the protocol and all subsequent amendments (Approval Number 17256). Written informed consent was obtained from each participant before enrollment into the study.

Results and Discussion

Patient characteristics data

A total of 102 patients were enrolled (SSPCA, n = 51; SBN, n = 51). The study groups did not differ in demographic characteristics (Table 1).

Characteristics	SSPCA (n = 51)	SBN (n = 51)	Total (n = 102)
Age (Years)			
n	50[a]	51	101[a]
Mean (SD)	37.52 (12.92)	36.31 (11.84)	36.91 (12.34)
Median	37.50	33.00	35.00
Minimum	18	18	18
Maximum	59	57	59
Gender, n (%)			
Male	25 (49.02)	19 (37.25)	44 (43.14)
Female	26 (50.98)	32 (62.75)	58 (56.86)

Table 1: Basic demographic information of the participants. [a]Date of birth for one patient in the SSPCA group was missing. SSPCA: Stérimar Stop and Protect Cold for Adults, SBN: Stérimar Blocked Nose.

Product usage, compliance and dropouts

One hundred patients completed the study: SSPCA, n = 51; SBN, n = 49 (lost contact with one patient, another patient discontinued the treatment due to non-product-related reasons). Five more patients were excluded from the PP analyses (2 in SSPCA group, 3 in SBN group) for using rescue medication other than the one allowed in the protocol, antihistamines or nasal steroids (Figure 2). In terms of product use, the differences between groups were not significant (Table 2).

	SSPCA (n = 51)	SBN (n = 51)	p-value
Mean number of days of product use	9.4	10.5	>0.05
Mean number of applications/day	2.96	2.98	>0.05
Mean volume per day (ml)	1.24	1.12	>0.05
Mean number of pulverizations/application	2.87	2.87	>0.05
Mean volume per application (ml)	0.41	0.38	>0.05

Table 2: Product use by groups during the study (ITT). SSPCA: Stérimar Stop and Protect Cold for Adults, SBN: Stérimar Blocked Nose.

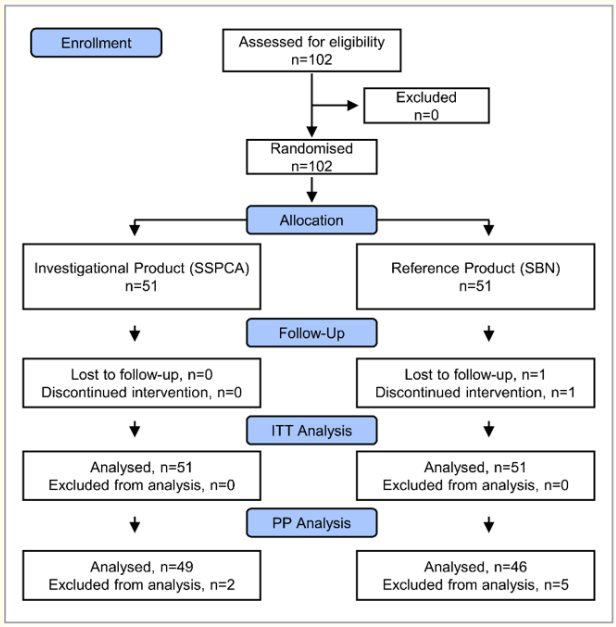

Figure 2: Flow diagram of the progress through the phases of the study. ITT: intention-to-treat; PP: per protocol.
118 x 220 mm (600 x 600 DPI).

Illness severity

The benefits of saline irrigation for symptomatic relief of upper respiratory tract infections including nasal discharge, congestion, sneezing, headache and sore throat were previously described in a systematic review which analyzed 5 randomized controlled trials on 749 subjects (544 children and 205 adults) [19].

The benchmark hypertonic seawater solution used in this study, SBN, has been previously shown to be more effective than isotonic seawater solution in eliminating symptoms of chronic rhinosinusitis such as nasal congestion, rhinorrhea, cough, headache and waking up during the night with no adverse events (15-day treatment in 60 chronic rhinosinusitis patients). The same study also demonstrated that the quality of life of patients in the hypertonic seawater solution group improved earlier in time compared to the isotonic seawater solution group [15]. Another study on healthy subjects has shown that nasal irrigation with a buffered hypertonic solution improves mucociliary clearance rates, while normal saline did not have the same effect [20].

In the present study the mean score for illness severity was calculated by summing 19 out of 21 items of the WURSS-21 questionnaire reported by subjects from the beginning to the end of the study divided by the number of days the diary was filled by the subject. Data analyzed both on ITT or PP populations revealed that there were no statistically significant differences in performance of the two products regarding illness severity, "today's score on global illness severity" (answer to question "How sick do you feel today?"), and "improvement since yesterday" (answer to question "Compared to yesterday, I feel that my cold is…") (Table 3).

These data indicate that both SSPCA (a hypertonic solution enriched with hyaluronic acids of different molecular weights, Caprylyl/Capryl glucoside, eucalyptus oil, and copper and manganese salts) and SBN (a hypertonic seawater solution enriched with copper and manganese salts) are equally efficient in terms of illness severity reduction.

Illness duration and rescue medication

It has been reported that the mean duration of the common cold is generally 7-10 days [17]. When analyzed on both ITT and PP populations, differences in illness duration, as measured by the mean number of days patients used the products (Table 4) were not statistically significant between groups. Our study shows that the mean illness duration for the whole study group was 7.44 days (SSPCA, 7.20 ± 4.12 days; SBN 7.70 ± 3.85 days) consistent with previous reports [17].

Mean score (SD) - ITT population			
	SSPCA (n = 51)	**SBN (n = 50)[c]**	**p-value**
Illness severity[a]	22.80 (17.95)	21.64 (13.38)	0.84
Today's score on global illness severity[b]	2.15 (1.27)	2.12 (1.08)	0.84
Improvement since yesterday[b]	2.60 (0.77)	2.74 (0.74)	0.37
Mean score (SD) - PP population			
	SSPCA (n = 49)	**SBN (n = 46)**	**p-value**
Illness severity[a]	22.37 (17.13)	21.69 (13.83)	0.85
Today's score on global illness severity[b]	2.16 (1.27)	2.07 (1.05)	0.99
Improvement since yesterday[b]	2.61 (0.77)	2.71 (0.75)	0.59

Table 3: Illness severity - WURSS-21 scores evaluated by the subjects during the study. [a]: Mean of score sums during diary filling. [b]: Mean of scores during diary filling. [c]: One subject was lost to follow-up. SSPCA: Stérimar Stop and Protect Cold for Adults, SBN: Stérimar Blocked Nose, ITT: intention-to-treat, PP: per protocol.

Rescue medication was used by 3 patients in the SSPCA group and 4 patients in the SBN group. Mean number of days of rescue medication use was 1.60 ± 0.57 and 2.25 ± 0.95 for SSPCA and SBN groups, respectively (p = 0.45).

Patient satisfaction

As per the diaries the patients filled during treatment, the mean patient satisfaction score for SSPCA was 7.32 ± 1.78 and the mean product acceptability score was 7.65 ± 1.88 out of a 10-item Likert scale. No statistically significant differences were observed between SSPCA and SBN. Both products were well accepted by the patients who also declared willingness to use them again in the future (Table 4).

Additional outcome variables

In terms of speed of action, patients reported a quicker effect with SSPCA than with SBN for decongesting the nose (p = 0.0029),

ITT population			
	SSPCA (n = 51)	**SBN (n = 51)**	**p-value**
Illness duration - Days - Mean (SD)	7.20 (4.12)	7.70 (3.85)	0.47
Patient satisfaction - Likert Scale - Mean (SD)	7.32 (1.78)	7.58 (1.71)	0.47
Patient acceptability - Likert Scale - Mean (SD)	7.65 (1.88)	7.80 (2.13)	0.50
Willingness to use the product in the future Yes = 1; No = 2 - Mean (SD)	1.00 (0.00) n = 13	1.00 (0.00) n = 8	1.00
PP population			
	SSPCA (n = 47)	**SBN (n = 42)**	**p-value**
Illness duration - Days - Mean (SD)	7.36 (4.14)	7.69 (3.95)	0.62
Patient satisfaction - Likert Scale - Mean (SD)	7.29 (1.80)	7.65 (1.62)	0.36
Patient acceptability - Likert Scale - Mean (SD)	7.61 (1.91)	7.74 (2.19)	0.54
Willingness to use the product in the future Yes = 1; No = 2 - Mean (SD)	1.00 (0.00) n = 13	1.00 (0.00) n = 8	1.00

Table 4: Illness duration and patient acceptability scores as evaluated study participants. SSPCA: Stérimar Stop and Protect Cold for Adults, SBN: Stérimar Blocked Nose, ITT: Intention-to-treat, PP: Per protocol.

relieving other common cold symptoms (p = 0.0321) and allowing easier breathing (p = 0.0125) as evaluated during the first 7 days of treatment (Figure 3) at 1 min (left panel) and 2 min (right panel) after application.

In addition, after the second day of application, patients reported more effectiveness (p = 0.0031) and a significantly higher performance with SSPCA than with SBN in improving common cold symptoms (p = 0.0002) (Figure 4).

Finally, significantly more patients reported SSPCA than SBN in improving nasal well-being (p = 0.0279); and feeling of protection of the nose from external aggressions (p = 0.022) and perceived formation of a layer on the nasal mucosa (p = 0.0127) as measured over the first 7 days of application (Figure 5).

The observed superiority of SSPCA may be attributed to the molecules used to enrich the seawater in the formulation of SSPCA. Hyaluronic acid is an extracellular matrix component with film-forming action and is involved in healing of the wounds that may occur on the nasal mucosa during a common cold episode [21,22]. Eucalyptus has been shown to have antimicrobial effects against a wide range of pathogens that cause respiratory infections, and to stimulate trigeminal cold receptors in the nasal mucosa, improving the perception of air entrance through the nostrils, thus contributing to patient´s satisfaction and well-being [23,24]. Copper and manganese have been demonstrated to stimulate the body's self-defense mechanisms [25,26].

Over the first seven days of treatment, no significant differences were detected between the products for hydrating (p = 0.84),

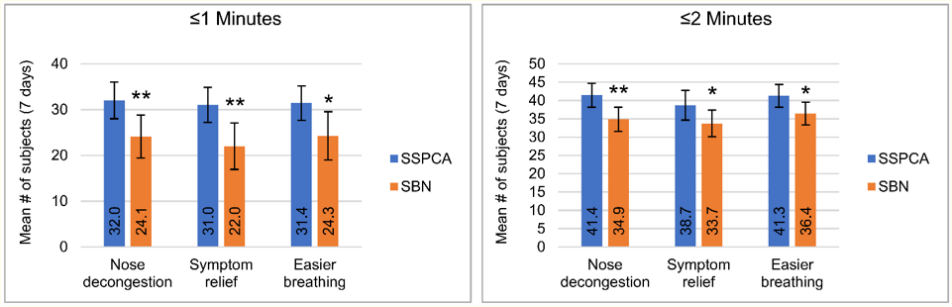

Figure 3: Average number of subjects who reported an improvement for the symptoms at the indicated (or shorter) time points. *p < 0.05 and **p < 0.01. SSPCA: Stérimar Stop and Protect Cold for Adults; SBN: Stérimar Blocked Nose.
179 x 59 mm (600 x 600 DPI) .

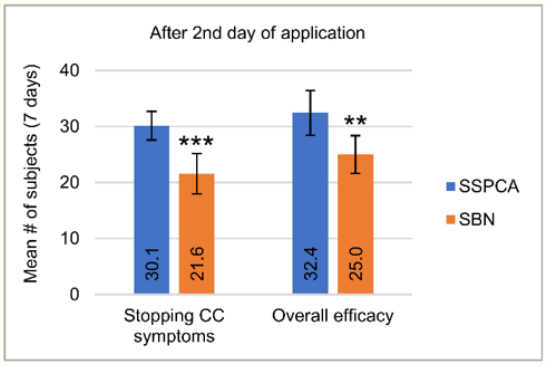

Figure 4: Number of subjects who reported overall efficacy and improvement of common cold symptoms after the second day of application. **p < 0.01 and ***p < 0.001. SSPCA: Stérimar Stop and Protect Cold for Adults; SBN: Stérimar Blocked Nose.
86 x 57 mm (600 x 600 DPI).

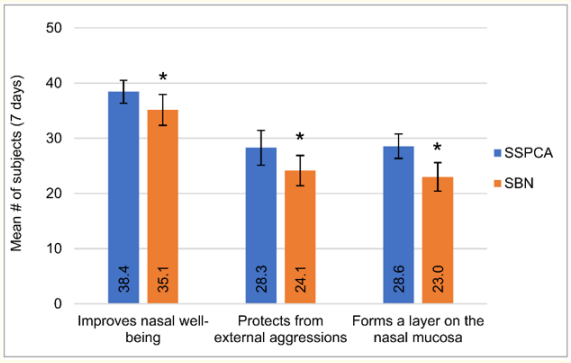

Figure 5: Mean number of subjects who reported the perceived effects over the first 7 days of treatment. *p < 0.05. SSPCA: Stérimar Stop and Protect Cold for Adults; SBN: Stérimar Blocked Nose.
112 x 70 mm (600 x 600 DPI).

soothing lastingly (p = 0.08), relieving lastingly (p = 0.36) and protecting lastingly (p = 0.25) the nasal mucosa (Figure 6).

More than 50 percent improvement has been observed for both products in symptom severity scores for runny nose, plugged nose and sneezing, and in quality of life scores for sleeping well and

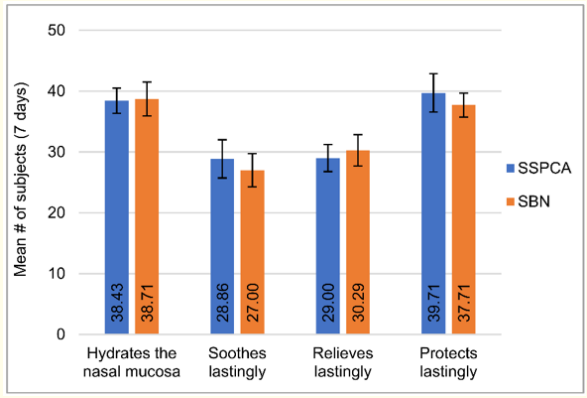

Figure 6: Number of subjects who reported the perceived effects over the first 7 days of treatment. SSPCA: Stérimar Stop and Protect Cold for Adults; SBN: Stérimar Blocked Nose.
105 x 71 mm (600 x 600 DPI).

breathing easily over the first 7 days of treatment. No statistically significant differences were observed between the two groups for these parameters (Figure 7).

Nasal swab evaluations

Samples collected at the initial and final visits were screened for pathogens (Figure 8). Results for influenza A, influenza B, bocavirus, adenovirus and rhinovirus were assessed by qRT-PCR, whereas the rest of the pathogens were below the detection limit at both visits. For each retrieved virus type, the levels of the viral particles were normalized to their levels at the beginning of the study (Visit 0). At Visit 0, no significant differences were observed in viral load levels between products. At Visit 1, significant decrease in the levels of virus were obtained (the viral particle levels were between $2.29x10^{-5}$ and $6.05x10^{-9}$ compared to the levels at visit 0). However, no significant differences were observed in viral load levels between products at Visit 1. Therefore, both products were equally efficient in minimizing the presence of viruses in the nasal swabs with no intergroup differences.

The presence of copper in both formulations can be beneficial in their activity against virus infections [27]. It has recently been demonstrated that surface stability of SARS-COV-2 is strongly inhibited by copper while plastic or stainless steel are not able to similarly inhibit surface stability, making copper itself a "necessary

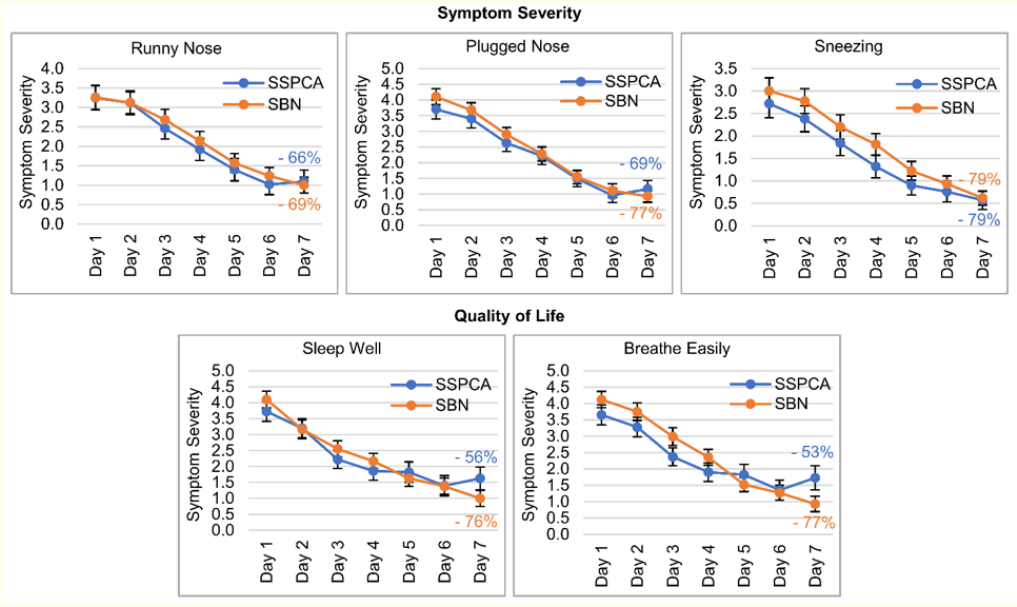

Figure 7: Self-evaluated mean scores of the attributes over the first 7 days of treatment. Error bars represent ± SEM. SSPCA: Stérimar Stop and Protect Cold for Adults; SBN: Stérimar Blocked Nose.
173 x 103 mm (600 x 600 DPI).

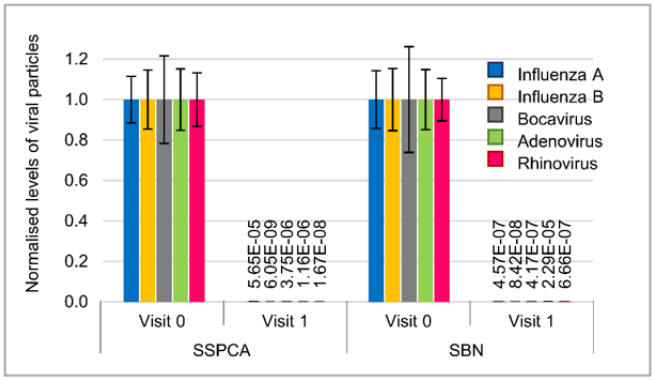

Figure 8: Normalised levels of viral particles detected by qRT-PCR in the nasal swab samples of subjects collected at the initial (Visit 0) and the final (Visit 1) visits. SSPCA: Stérimar Stop and Protect Cold for Adults; SBN: Stérimar Blocked Nose.
109 x 63 mm (600 x 600 DPI).

element" to control viral replication [28]. At the same time, an expert panel of ENTs has recently suggested that nasal irrigation with saline solution enriched with copper could be the right choice to inhibit and to prevent SARS-COV-2 viral replication [29]. Several publications on Stérimar copper-enriched formulas have demonstrated the safety and efficacy of these specific formulations which have been in use for a long time to treat the common cold [15,30]. However, the exact mechanism of a possible antiviral action remains to be explored in future research.

Safety

SSPCA and SBN were both well tolerated after 2 weeks, when used as instructed (two pulverizations/nostril when needed up to 6 times a day), as no patients reported any adverse event during the study.

Study limitations

There are some limitations in this study. The first limitation was using a benchmark product as control. Using a simple saline solu-

tion or isotonic seawater group as control would better highlight the benefits of the test product. Second, the majority of the participants stopped using the products after 7 days, when their symptoms resolved. Having them continuing using the product for the entire study period (14 days) would have generated a better dataset. Third, the data was mainly collected through self-reporting.

Conclusion

In summary, this double-blind, randomized, controlled clinical trial demonstrated that both SSPCA, a microfiltered hypertonic seawater solution enriched with hyaluronic acids, Caprylyl/Capryl glucoside, eucalyptus oil, and copper and manganese salts; and SBN, a microfiltered hypertonic seawater solution enriched with copper and manganese salts, are effective in reducing illness severity in common cold patients. Analyses on the subjective evaluation of the efficacy of products indicate that SSPCA has a faster onset of action compared to SBN in nasal decongestion, symptom and breathing relief, improving common cold symptoms and nasal well-being. Additionally, more patients quoted SSPCA as protecting from external aggressions and forming a layer on the nasal mucosa. The clinical roles of eucalyptus oil, hyaluronic acid, copper and manganese salts as an addition to seawater solution should be further investigated.

Therefore, SSPCA appears as a safe solution that provides faster symptomatic relief than SBN for patients with common cold.

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Conflict of Interest

AS worked formerly as EU Technology and Innovation Manager at Church and Dwight, Co., Inc. who owns the Stérimar brand. The authors report no other conflicts of interest in this work.

Data Sharing

Study protocol and Individual participant data that underlie the results reported in this article will be available to share in a Microsoft Excel table format after 6 months and ending 5 years following article publication. The data will be shared with researchers who provide a methodologically sound proposal for their meta-analysis. Proposals should be directed to the corresponding author of this publication (josip.culig@zvu.hr). To gain access, data requestors will need to provide a data access agreement. Data will be available for 5 years to be supplied via email.

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