Research Article

CLINICAL INVESTIGATION

Clinical efficacy and safety of a long acting osmotic nasal filmogen spray for the treatment of rhinosinusitis

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Abstract

Objective: Rhinosinusitis is the most common diseases affecting nearly 10%-15% world population. The physiopathology is multifactorial involving nasal mucosa inflammation, cellular damage, and obstruction of sinus drainage due to bacterial biofilm on the sinus openings. Currently available chemical or biological treatments are mono-target and may have serious side effects in sensitive population. We evaluated the clinical efficacy of NESOSPRAY HE-G nasal spray, a new generation of safe, multi-target, non-irritant, osmotic, polymeric glycerol film for the treatment of rhinosinusitis in adults, including pregnant women, against placebo spray as control.

Methods: A 15-day, randomized, placebo-controlled, double-blind, efficacy and safety clinical study was conducted in 12 males and 8 females in the placebo group and 9 males and 11 females in NESOSPRAY HE-G group, with 7+7 pregnant women in each group suffering from acute rhinosinusitis. 2 nasal sprays were applied 3 to 4 times a day for 15 consecutive days. Effects on rhinorrhoea or congestion, fever, cough, sleep, and facial pain were recorded at baseline, 2 h after 1st treatment, and on day 1, 2, 3, 6 and 15. The need for antibiotics as well as adverse effects was also recorded.

Results: Both NESOSPRAY HE-G and nasal rinses with placebo spray reduced rhinosinusitis symptoms, but the reduction was much faster and stronger in the test group compared to the placebo group. The efficacy of NESOSPRAY HE-G treatment was highly significant *vs* placebo on all parameters right from day 2. Due to the rapidity of effects of NESOSPRAY HE-G, only 1/20 patients in this group required antibiotherapy *vs* 15/20 in the placebo group. No adverse effects were observed, including in pregnant women.

Conclusions: To avoid the use of chemical, biological, and mono-target drugs for the treatment of rhinosinusitis, a mechanically acting, totally safe, rapid and multi-target treatment represents a breakthrough discovery for the treatment of rhinosinusitis in both adults and childbearing women.

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Keywords: Rhinosinusitis • Bacterial biofilm • Pregnant women • Filmogen polymeric glycerol • Clinical • Nesospray HE-G

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Abbreviations

RS: Rhinosinusitis
EPOS: European Position Paper on Rhinosinusitis
RSSS: Rhinosinusitis Symptom Score
AEs: Adverse Events
SAEs: Serious Adverse Events

Introduction

Rhinosinusitis (RS) is a clinical syndrome involving inflammation of the mucous membranes of the nasal cavities and sinuses, with an estimated prevalence of 10%-15% of the population in the Western world [1]. The 2012 European Position Paper on Rhinosinusitis (EPOS) guidelines describe RS as an inflammatory condition defined by the presence of two or more cardinal symptoms (rhinorrhoea or nasal congestion, fever, cough, and facial pain on pressure for at least 4-weeks [2]. For inclusion in a clinical trial, the guidelines require that the mean scores of these key symptoms be assessed on a defined scale and that a minimum mean Rhinosinusitis Symptom Score (RSSS) be established as a primary criterion [3].

Patients may also experience coughing, bad breath, irritability, low energy, swelling around the eyes and thick yellow-green nasal or post-nasal discharge [3]. Sinusitis usually starts after an ostial obstruction [4]. This obstruction causes negative pressure in the sinus, resulting in fluid leaking into the sinuses [5]. This fluid is a favoured culture medium that is easily infected and is the main cause of RS. In the early stages, the disease is easily treated with anti-inflammatory drugs and antibiotics, but if the infection is not stopped, micro-organisms enter the sinuses and start to multiply. Bacteria and fungi form a symbiotic relationship to protect themselves against all aggressions: the sessile planktonic bacteria adhere to the sinus surface, secrete protective extracellular matrix and form 3-dimensional biofilm aggregates of microorganisms [6,7]. The rigidity of these biofilm aggregates increases over time, damaging the sinus mucosa and potentially impeding sinus clearance. Biofilms are 10-1000 times more resistant to antimicrobial agents than planktonic bacteria because they form a strong physical barrier to any external attack. Sinus infection and inflammation leads to increased intra-sinus pressure, facial pain, headaches and occasionally the development of polyps in the nasal cavity [8]. Treatment becomes very difficult because the sinuses are closed cavities with poor blood circulation, and no treatment in pharmacologically active concentrations can reach the sinus. RS is even more difficult to treat in children and women of childbearing age [9]. Pregnancy rhinitis is a major cause of RS in pregnancy. Approximately 20%-40% of women of childbearing age report symptoms of rhinitis, and approximately 10%-30% of these patients experience worsening symptoms during pregnancy, especially in the presence of asthma [10,11]. The diagnosis and management of acute or chronic RS during pregnancy pose unique challenges to the otolaryngologist, as almost all existing treatments are chemical, and their toxic, mutagenic or teratogenic potential is not always clearly assessed [12,13]. However, according to the International Statistical Classification of Diseases and Related Health Problems, less than 2% of people with rhinosinusitis seek medical help. This is mainly due to the lack of an effective and safe treatment that can reach the sinuses and apply sufficient pressure to the sinus-blocking film to open and drain the sinuses without damaging the nasal mucosa, the most sensitive organ in our body [14,15].

The most used treatments for RS nowadays include oral or topical corticosteroids, antihistamines, antibiotics, anti-leukotrienes, decongestants, and immunotherapy, with or without other concomitant treatments [16]. Unfortunately, all these treatments, except for saline irrigation, are chemical and have adverse effects, especially in children and pregnant women. For example, corticosteroids are not considered safe during pregnancy except after the first trimester and are only used in severe CRS (Chronic RS), particularly in asthmatics, when topical corticosteroids such as budesonide, fluticasone and mometasone are not effective [17]. Oral antibiotics are also commonly used during pregnancy, but long-term use of macrolides is not recommended, while tetracyclines, aminoglycosides, trimethoprim-sulfamethoxazole and fluoroquinolones are not considered safe [18,19]. Similarly, anti-leukotrienes are not recommended except in cases of recalcitrant asthma during pregnancy [20]. Oral decongestants can be used in severe cases, but first-generation antihistamines should be avoided because of their sedative and anticholinergic properties [21,22]. The most recommended and safest treatment remains nasal irrigation with saline or salt solutions, which acts as an osmotic solution to cleanse the nasal mucosa of impurities.

In the absence of any other safe treatment, nasal irrigation with isotonic saline 0.9% NaCl remains the treatment of choice as it helps to clear the nasal passage, facilitates breathing, and improves ciliary movements [14]. Unfortunately, such treatments are not very effective because of the short duration of action, the fact that normal saline is neither osmotic nor filmogen, and the need for repeated nasal rinses to achieve mild to moderate improvement. Given this unmet medical need for the treatment of RS and CRS, we envisioned a completely new strategy to develop a hypertonic, long-lasting polymeric film capable of generating a strong positive osmotic pressure across the nasal mucosa to keep the nasal surface clean of free-floating contaminants and to

open the sinuses by applying continuous mechanical osmotic pressure across the sinus orifices [23,24]. This type of multi-target treatment should be completely safe and almost instantaneous.

To achieve these goals, we developed a glycerol-based solution because glycerol is almost 18 times more osmotically active than 3.2% to 3.4% NaCl seawater. Glycerol is a natural antiseptic and cell-friendly solution. Its properties make glycerol an ideal candidate that can apply sufficient osmotic pressure across semi-permeable living biological membranes without irritating the nasal mucosa or being cytotoxic to already damaged cells [25]. However, when applied to a living biological membrane such as the nasal mucosa, the osmotic activity generated by the film causes a strong hypotonic fluid flow from the mucosa towards the film, leading to immediate dilution of the film and loss of osmotic activity within a few minutes. As certain inert and large polymers (e.g. plant tannins) are known to bind to selected macromolecules (H, OH binding) and specific proteins, after pre-screening we selected 82 natural and synthetic polymeric structures to find those that could bind to glycerol molecules to make the glycerol film stable. The irritation potential of glycerol was adjusted by combining appropriate glycerol concentrations with thickening and gelling ingredients [26,27].

Our postulate was that topical application of such a solution over the nasal mucosa should attract hypotonic fluid from the semipermeable membranes and remove free-floating contaminants from the nasal surface. Such an osmotic film should be non-irritant and resistant to the mechanical pressure exerted during osmotic flow. The clinical efficacy of this filmogen polymeric osmotic film is evaluated in comparison to a placebo spray in adults, including pregnant women.

Material and Methods

Test products (NESOSPRAY HE-G and Placebo)

The test product was a slightly viscous, transparent filmogen liquid containing glycerol, aqua, hydroxypropylcellulose, Rhinocyanidin polymeric mix (derived from extracts of *Camellia sinensis, Vaccinium myrtillus, Vaccinium macrocarpon,* and *Sambucus nigra*) together with essential oils of *Eucalyptus globulus, Mentha piperita, Rosmarinus officinalis* and *Thymus satureioides* to enhance olfactory properties. The resulting solution was called NESOSPRAY HE-G (HE-G).

The placebo was composed of water with acacia and xanthan gums, and potassium sorbate, sodium benzoate, citric acid as preservatives. The test product and placebo were presented identically in 15 ml plastic vials, fitted with a nasal spray for topical application. Texture, color and mode of were identical to the test product.

Clinical study organization: The trial was conducted between 2021-2023 at Mudra Clinical Research, India (ISO-14155 certified clinical research organization, Registration N° SQ18N02, dated 05/09/2018, renewed up to 04/04/2021). The protocol and study design were approved by the Institutional Ethics Committee Ethicare, India. (Reg. No. ECR/224/Inst/MH/2015/RR-21, dated 07/08/2018). The trial was registered under N° CTRI 2023/02/079396 on 11/06/2023.

The study was conducted in accordance with the "Declaration of Helsinki", concerning medical research in humans (Brazil, October 2013), and following the ICH-GCP guidelines. Written informed consent was obtained from all the patients.

Study design and rationale: The study was designed as a comparative, randomized, double-blind, parallel-group, observational study to evaluate the efficacy and safety of Rhino-sinusitis nasal spray NESOSPRAY HE-G versus placebo nasal spray in the treatment of acute rhinosinusitis.

The study duration and doses were selected based on previous clinical trials with hypertonic filmogen nasal sprays for different indications, where these products were used as 2 sprays per nostril for each application, 3 times a day for 15 days [28,29]. The number of patients enrolled was defined based on the minimum number of patients required in this type of study to obtain statistically comparable data between the two groups (Alpha power 95%).

Inclusion and exclusion criteria: At enrolment, patients underwent a physical examination, and their medical, surgical and allergic history was reviewed and recorded. Vital signs such as blood pressure, pulse and respiratory rate were recorded. 45 patients without serious pathology were then enrolled for randomisation. The main inclusion criteria were:

- Adults, men and women over 18 years of age.
- Participants with complaints of clinical manifestations of Rhinosinusitis (RS) with major symptoms (rhinorrhoea or nasal congestion, fever, cough, pain on facial pressure).

- Patients with a mean Rhino-Sinusitis Severity Score (RSSS) = or >25 out of a maximum score of 50.
- Participants willing to refrain from using any other medication or face masks that could influence the study outcome.
- Not using any medication containing antibacterial, antiviral, antihistamine or steroid for 2 weeks prior to screening.
- Able to understand and follow the protocol until the end.

Primary exclusion criteria included potential allergy risks associated with any of the composition's ingredients, individuals with chronic respiratory problems, particularly bronchopneumonia, recent nasal surgery and patients receiving immunosuppressive therapy.

Randomization: We planned to screen about 45 patients, to recruit minimum 18 men and 18 women in the study with at least 50% pregnant women. After screening, patients who met all inclusion criteria were enrolled and randomly assigned in a 1:1 ratio to receive either placebo control (R) or NESOSPRAY HE-G test product (T). Treatments were allocated to patients by randomization using SAS version 9.1.3 according to a randomization schedule. Block randomization was used to generate the list. Within the block, treatments were allocated in a 1:1 ratio as described above. Each patient was given a unique screening identification number, a randomization code, and an enrolment identification number.

The purpose of the study, safety guidelines, ethical standards, study design, and scoring of symptoms and adverse events were explained to each patient before written consent was obtained. Patients were asked to apply the allocated treatment in each nostril from day 1 to day 15 or until complete recovery, whichever came first. The first treatment was administered immediately after the patient's enrolment in the study (day 1).

Parameters studied: The primary outcome was to evaluate the change in RSSS from baseline to 2 h post first dose initiation on day 1, then on day 3, day 6, and day 15.

RSSS is a tool used to assess the severity of rhinosinusitis, whether acute or chronic. This score helps quantify the impact of symptoms on the patient. It considers various aspects of the disease, including the intensity and frequency of symptoms, as well as their impact on the patient's quality of life. The Rhino-sinusitis Severity Score includes assessment of the following symptoms on an analogue scale from 0 to 10: Rhinorrhoea, nasal congestion, cough, sleep disturbance, sinus pain on pressure and fever.

Key secondary endpoints included change in individual symptom scores, proportion of patients requiring antibiotics or other medications in worst cases, adverse effects, global patient and investigator assessment and product acceptability at the end of the study.

Statistical analysis of data: Statistical analysis of data collected during the 15 day study period was performed to assess differences between the R and T groups.

Demographic variables including sex, age, weight, height, BMI and pregnancy status were analyzed for homogeneity between groups using Student's t-tests, Wilcoxon rank-sum tests and Fisher's exact tests. Where appropriate, boxplots were also used to visualize group differences.

The difference in mean scores between the R or T groups at different time points was analyzed using two-way ANOVA with interaction on mixed linear models. The "Sum of Squares" (Sum Sq) is used to measure the total variation in the data. The F-value (F) is used to determine the significance of the effect. Post-hoc tests (t-tests or Wilcoxon tests (W)) were performed to detect significant score differences between treatments on specific days.

To assess differences in 'yes' or 'no' responses for adverse effects between the T and R groups, the chi-squared test was used to examine the association between treatment and adverse effect responses. Hypotheses were tested for independence between variables, with conclusions based on chi-squared statistics and degrees of freedom.

Results

Demographics: A total of 46 patients, including men and women, were screened and 42 were retained after randomization to receive R (placebo) or T (NESOSPRAY HE-G) treatment. 2/42 patients withdrew from the study due to non-compliance with the study protocol. At the end of the study, 20 patients (12 males and 8 females) in the R group and 20 patients (9 males and 11 females) in the T group completed the study protocol. Of the 19 women in the study, 14 were in various stages of pregnancy, 7 in each group. The comprehensive analysis of demographic characteristics, including sex, distribution, age, height, weight, IBM scores, current symptom scores and pregnancy incidence, between the R and T groups showed no statistically significant differences between the two groups.

The Fisher's exact test for gender distribution and pregnancy yielded a non-significant p-value of 1. This indicates that there was no discernible difference between the two groups in terms of male and female representation and pregnancy. In addition, two-sample t-tests for age, height, weight and BMI scores show no significant difference of means between the groups.

The Wilcoxon rank sum test for current symptom scores also failed to reject the null hypothesis, indicating that there was no significant shift in position (median) between the groups. Taken together, these findings underscore the absence of demographic and inclusion criteria differences between the two groups across a range of factors, highlighting the homogeneity of the demographic characteristics examined (Table 1).

Table 1: The demographic characteristics of the patient population. Quantitative parameters are presented as mean ± SD. Statistical analysis was performed by two-sided Wilcoxon rank or Student tests to compare the means of the two groups. A Fisher's exact test was performed for the male-female proportions and pregnant female between groups. The demographic characteristics of R and T groups are comparable.

	Total	Group R	Group T	p-value
Men (n)	21	12	9	1.000 (NS)
Woman (n)	19	8	11	1.000 (NS)
Mean Age	28.82 ± 10.16	28.9 ± 9.97	28.75 ± 10.60	0.964 (NS)
Mean Weight	57.62 ± 7.36	58.15 ± 8.21	57.1 ± 6.58	0.658 (NS)
Mean Height	156.14 ± 7.69	156.68 ± 8.28	155.6 ± 7.24	0.663 (NS)
Mean BMI	23.56 ± 1.62	23.60 ± 1.81	23.52 ± 1.45	0.875 (NS)
Pregnant Woman	14	7	7	1.000 (NS)
Duration of RS at baseline	4.825 ± 0.958	4.9 ± 0.96	4.75 ± 0.96	0.723 (NS)
RSSS at baseline	30.79 ± 2.82	31.24 ± 0.96	30.57 ± 3.20	0.628 (NS)

Primary endpoint

RSSS demonstrates significant findings in the effectiveness of NESOSPRAY HE-G. The main effect of treatment on the RSSS is highly significant ($F(1, 40) = 64.719$, $p = 6.873 \times 10^{-10}$), indicating substantial differences in mean scores between the Treatment groups (R and T). This suggests that the type of treatment administered significantly influences the overall RSSS (Table 2).

Table 2: Mean RSSS which takes into account the means of rhinorrhoea, nasal congestion, cough, sleep disturbance, sinus pain on pressure and fever, in R and T groups at BL, 2 h after first treatment on day 1, and on day 2, 3, 6, and 15, calculated using 2-way repeated measures ANOVA. The difference between R and T groups are highly statistically different ($p<0.001$) right from day 2.

Day of treatment	Group R	Group T	p-value
BL	30.9 ± 2.45	30.45 ± 3.23	NS
2 h	31.2 ± 2.44	29.9 ± 2.5	NS
Day 2	29.9 ± 2.31	23.1 ± 1.94	p<0.001
Day 3	27.6 ± 2.45	20.35 ± 1.53	p<0.001
Day 6	19.9 ± 1.76	13.7 ± 2.69	p<0.001
Day 15	1.8 ± 1.15	0.15 ± 0.67	p<0.001

Furthermore, the main effect of the day of assessment is also highly significant ($F(5, 200) = 1917.036$, $p < 2.2 \times 10^{-16}$), showing that the scores vary significantly across different observation days. This highlights that the timing of assessment plays a crucial role in understanding the effectiveness of treatments over the course of the study. The results were significantly in favour of NESOSPRAY HE-G after day 1 ($p<0.001$). This effect persists significantly throughout the treatment.

In summary, the RSSS shows that treatment type has a significant effect on the symptom scores, with differences becoming more pronounced over time. This positive effect favors the NESOSPRAY HE-G treatment from the second day of treatment.

Secondary endpoints

Effect on rhinorrhoea and nasal congestion: Rhinorrhoea was severe in both groups at baseline. Bilateral Wilcoxon test analyses between the two treatments showed no significant difference in mean scores at BL ($W = 185$, p-value $= 0.6755$), indicating homogeneity of intensity between the two groups at BL and even after 2 hours of treatment ($W=262.5$, p-value 0.07072). The 2 h post-dose results on day 1 suggest that none of the treatments helped to reduce rhinorrhoea or nasal congestion within 2 h of the first treatment (Table 3).

Table 3: Mean scores of rhinorrhoea/nasal congestion in total population (n=20+20 in R and T groups) at BL, after 2 h of 1st treatment and after 2, 3, 6, and 15 days of treatment. Mean values were compared between R and T using ANOVA and t-test at each time point.

Day of treatment	Group R	Group T	p-value
BL	6.85 ± 0.81	6.95 ± 0.75	NS
2 h	7 ± 0.72	6.55 ± 0.75	NS
Day 2	6.65 ± 0.67	4.75 ± 0.85	p<0.0001
Day 3	5.95 ± 0.68	4.25 ± 0.63	p<0.0001
Day 6	4.4 ± 0.59	3.4 ± 0.68	p<0.0001
Day 15	0.7 ± 0.57	0.0 ± 0.0	p<0.0001

After 2 days of treatment, there was a statistical-ly significant difference between the two groups (W =382, p-value =4.189 × 10^{-7}), with lower mean scores in T vs R, suggesting a significant reduction in rhinorrhoea/nasal congestion in the T active treat-ment group compared to the R control group. This reduction in the T group persisted after 3 days with a significant shift in scores (W =382.5, p-value =3.349 × 10^{-7}), indicating a sustained effect of treatment on the observed outcomes. After 6 days, this was fur-ther accentuated (W=336, p-value =7.204×10^{-5}), highlighting a constant and intensifying effect of treatment T compared to R. Finally, after 15 days, the Wilcoxon rank sum test revealed a significant difference in scores (W =330, p-value =1.764 × 10^{-5}), indicating a sustained and cumulative effect of treat-ment T compared to R.

Effect on cough: Cough intensity was high in both R and T groups at BL and remained unaffected in both groups 2 h after the first treatment. On day 3, 6 and 15, a progressive and significant reduction in cough intensity was observed in both groups, but this re-duction was much faster in the T group than in the R group (p<0.001). From day 2, the difference between the R and T groups was statistically significant until the end of the study. On day 15, there was no cough-ing in the T-treated patients, while some coughing was still present in the R-treated population. These results reflect a progressive, rapid, time-dependent and sustained effect of T treatment, with a signif-icant reduction of coughing in T vs R from day 2 (Table 4).

Table 4: Mean scores of cough intensity in total population (n=20+20 in R and T groups) at BL, after 2 h of 1st treatment and after 2, 3, 6, and 15 days of treatment. Mean values were compared between R and T using ANOVA and t-test at each time point.

Day of treatment	Group R	Group T	p-value
BL	6.6 ± 0.88	6.8 ± 0.95	NS
2 h	6.85 ± 0.87	6.6 ± 0.75	NS
Day 2	6,7 ± 0.92	5.2 ± 0.69	p<0.0001
Day 3	6.15 ± 0.98	4.75 ± 0.55	p<0.0001
Day 6	4.45 ± 0.68	2.85 ± 0.81	p<0.0001
Day 15	0.35 ± 0.48	0.05 ± 0.22	p<0.1

Effect on fever: Almost half the patients had mild to moderate fever at BL, which remained identical in both groups until day 1. The mean intensity of fe-ver was reduced slightly faster in T compared to R on day 2 (p<0.1) and day 3 (p<0.001). Thereafter, the intensity of fever decreased progressively in both groups until the end of the study, but the difference was not statistically significant. It is concluded that the reduction of fever in T group was slightly better versus R (Table 5).

Table 5: Mean fever scores in R and T groups at BL, 2 h post 1st dosing, and on days 2, 3, 6, and 15. NS signifies not statistically significant.

Day of treatment	Group R	Group T	p-value
BL	3.9 ± 1.20	3.85 ± 1.03	NS
2 h	4.05 ± 1.14	4.05 ± 0.75	NS
Day 2	3.85 ± 0.98	3.05 ± 0.75	p<0.1
Day 3	3.8 ± 0.95	2.7 ± 0.80	p<0.001
Day 6	1.95 ± 1.39	1.35 ± 1.30	NS
Day 15	0.05 ± 0.22	0.0 ± 0.0	NS

Facial pain on pressure: This is one of the main complaints of sinusitis. When the sinuses are clogged with bacterial biofilm, the sinus pressure continues to rise, and the inflammation of the sinus wall manifests itself as facial pain on pressure. Until the sinuses are opened and drained, the pain continues. As shown in table 6, neither R nor T treatment modified sinus pain intensity up to 2 h after the first dose, but from 2 days of treatment, a statistically significant difference was observed in T (W =328.5, p-value =0.001 *vs* R), which continued day 3. The reduction in pain intensity continued in both groups up to day 15, but the rate and intensity of reduction was much faster in T *vs* R (W =360.5, p<0.0001), suggesting a sustained and escalating effect of T *vs* R with time. There was almost no facial pain on pressure in both groups on day 15.

Table 6: Mean scores of facial pain intensity upon pressure in the total population (n=20+20 in R and T groups) at BL, after 2 h of 1st treatment and after 2, 3, 6, and 15 days of treatment. Means were compared between R and T using ANOVA and t-test at each time point.

Day of treatment	Group R	Group T	p-value
BL	7.1 ± 0.78	6.7 ± 1.08	NS
2 h	6.8 ± 1.10	6.6 ± 1.14	NS
Day 2	6.35 ± 0.87	5.1 ± 1.02	p<0.001
Day 3	5.8 ± 0.83	4.65 ± 0.74	p<0.001
Day 6	4.75 ± 0.78	3.1 ± 0.96	p<0.0001
Day 15	0.5 ± 0.51	0.05 ± 0.22	p<0.01

Effect sleep disturbance: RS markedly affects the quality of sleep, as shown in table 7, where the scores were about 6 on a scale of 10 at BL. Patients in group T had less sleep disturbances right from the second day of treatment up to the end of the study (p<0.0001 *vs* group R), which corresponds to im-provement in overall RS symptoms, observed from day 2 onwards. After 15 days of treatment there was no difference between R and T groups (NS) as rhi-nosinusitis symptoms fade with time.

Table 7: Mean scores (± SD) of sleep disturbances in R and T group patients evaluated on a scale of 0 to 10, where 10 indicates very poor sleep at BL, and on day 2, 3, 6, and 15 days of treatment. Means were compared between R and T using ANOVA and t-test at each time point.

Day of treatment	Group R	Group T	p-value
BL	6.45 ± 0.68	6.15 ± 0.93	NS
2 h	6.5 ± 0.69	6.15 ± 0.93	NS
Day 2	6.35 ± 0.59	5.0 ± 0.65	p<0.0001
Day 3	5.9 ± 0.64	4.0 ± 0.65	p<0.0001
Day 6	4.4 ± 0.75	3.05 ± 0.60	p<0.0001
Day 15	0.2 ± 0.41	0.05 ± 0.22	NS

Product safety: Safety was assessed by evaluating the number of patients reporting the occurrence of Adverse Events (AEs) and/or Serious Adverse Events (SAEs) during the study period. No AEs or SAEs were reported in any of the groups that could be considered related to product administration.

Impact on the need for antibiotics: For ethical reasons, the investigators were authorised to use antibiotics if they felt that the patient's condition was worsening and required antibiotherapy. Out of 20 patients in the R control group, 15 patients received antibiotics for 1 day (6/15), 2 days (4/15), 3 days (4/15) or 4 days (1/15), while only one patient in the T group received antibiotics for 2 days. It should be noted that in developing countries like India, the use of antibiotics for rhinosinusitis is very common as these drugs are not very expensive. The reason why only 1/20 patients in the T group required antibiotics is probably because most of the patients in this group started to recover from day 2 and were not at risk of developing chronic respiratory disease. These results show that treatment with NESOSPRAY HE-G helps to suppress the disease in its early stages and drastically reduces the subsequent need for antibiotics.

Efficacy in pregnant women: 14 women in different stages of pregnancy were included in the study to verify the difference of efficacy and safety of the treatment compared to adult men and women. All the parameters evaluated show no difference with respect to the efficacy and safety of NESOSPRAY HE-G or the placebo treatment used during pregnancy compared to other population included in the study (p<0.523). These results show that NESOSPRAY HE-G can be used without concern during pregnancy.

Global product evaluation: Patients rated the treatment efficacy on RS on a scale of poor, fair, good, very good or excellent. At the end of the study, out of 20 patients R group, 1 rated the product as excellent, 5 as very good, 7 as good, and 7 as fair, compared to 18/20 in T group, who rated the product excellent, 1 very good and 1 fair. The results reflect that the efficacy and safety of NESOSPRAY HE-G was rated much better than the placebo treatment.

Discussion

RS or CRS are among the most common and chronic diseases affecting 10%-15% of the world's population with an enormous impact on the quality of life of patients. In addition, CRS is a major economic burden to society due to sickness absence, absenteeism, and loss of productivity [30-32]. The disease can be infectious, allergic, or non-allergic, but in all cases, it involves sinus obstruction due to inflammation and high intra-sinus pressure, leading to multiple local or systemic complications [5,11].

Local complications are mostly due to the anatomical proximity of the sinuses to the surrounding structures. The orbit and skull base are the structures most closely related to the paranasal sinuses as they share the same bony margins. Complications usually occur when infection spreads to these areas due to anatomical proximity. Local complications of rhinosinusitis include mucocele, pre-septal cellulitis, orbital cellulitis, subperiosteal abscess, orbital abscess, osteomyelitis, meningitis, brain abscess, subdural empyema and venous sinus thrombosis. They occur in about 5%-10% of patients followed for sinusitis [33].

Problems are exacerbated in pregnant women due to changes in normal physiology during pregnancy, which usually resolve after delivery. The condition, known as gestational rhinitis, occurs in about one third of women with pre-existing allergic rhinitis with worsening of symptoms during pregnancy. Rhinitis during pregnancy can also lead to maternal morbidity and mortality [34,35].

As the cause of CRS is often difficult to determine, the treatment of rhinitis during pregnancy requires careful consideration, as most treatments are chemical and may affect the health of the foetus and the mother.

Existing treatments typically include topical or oral antibiotics, decongestants, steroids and anti-inflammatory drugs, which may have a variety of adverse effects, particularly during pregnancy [36]. The safety of newer options such as antifungals, anti-IgE, anti-IL5, new antihistamines, complementary and alternative medicines, immunosuppressant's, leukotriene inhibitors and proton pump inhibitors has not usually been evaluated in childbearing women and may prove dangerous. A new generation of topical and safe nasal treatments are emerging with highly promising results but their efficacy in vulnerable population is still requires confirmation [37].

With such a wealth of treatments available, one wonders why none of them really work and why we still don't have a cure for CRS. Only the safe options such as exercise, nasal irrigation, and positioning and nasal valve dilators are used, but these either clean the nasal surface or provide some physical relief without addressing the underlying cause of CRS [38].

In theory, it would be enough to open and drain the sinuses and keep the nasal cavity clean to allow natural healing, but the multifactorial physiopathology of RS, which involves not only the nasal cavity but also the blocked sinuses and inflammation, makes it difficult to treat with a single mono-target drug [27]. Saline nasal irrigation with high-volume, low-pressure delivery devices or multiple irrigations is still considered one of the best and safest treatments to alleviate RS symptoms, as these treatments may help to clear the nasal passages, improve respiration, ciliary beating or reduce the microbial load, thereby alleviating RS symptoms. Recent evidence clearly shows that bacterial biofilm, which obstructs sinus openings in up to 75% of patients, is the main cause of persistent CRS [39]. In the early stages of the disease (2-4 weeks), when the biofilm is not too robust, it can probably be disrupted by regular and frequent saline rinses or seawater containing 3.2%-3.4% NaCl (upper limits of cytotoxic concentration), but once it is well adhered to the mucosa and becomes stronger with time, it is highly resistant to any topical or systemic treatment and can only be removed mechanically [9,40]. In this study, we wanted to test the efficacy and safety of NESOSPRAY HE-G, a highly osmotic but stable film that can adhere to the nasal mucosa and keep the nasal surface free of contaminants by strong outward osmotic fluid flow. Strong osmosis should also help break down the sinus-blocking membrane and drain the sinuses without the use of chemical or biological drugs.

The results of this study show that treatment of normal adult population and pregnant women suffering from RS with placebo spray for 15 days provided certain symptomatic relief, minimising rhinorrhoea, nasal congestion, cough, facial pain and overall RS symptoms, but the improvement was slow and mild compared to the NESOSPRAY HE-G-treated patients. This is understandable as the placebo spray does not exert strong osmosis and the product stability on the nasal mucosa is poor [41,42]. It should be noted that in this study the placebo sprays were used regularly, which the case is not always when patients use the product under uncontrolled conditions. The NESOSPRAY HE-G treatment was found to be highly effective in terms of onset of action and suppression of overall symptoms. NESOSPRAY HE-G forms a long-lasting, highly osmotic film compared to placebo, which not only helps to keep the nasal mucosa free of contaminants, but also exerts continuous osmotic pressure on the sinus-blocking biofilms to help open and drain the

sinuses. Consequently, relieving intra-sinus pressure helps to reduce facial pain upon pressure.

The second reason for the relatively good efficacy observed with the placebo spray in this study is because almost all patients (19/20) in the placebo group received antibiotics, compared to only 1/20 patients in the NESOSPRAY HE-G group. As an osmotic cleansing solution, NESOSPRAY HE-G continuously removed microbial contaminants, acting as a mechanical antimicrobial and avoiding the need for chemical antibiotherapy. It should be noted that cleaning the nasal sinuses and keeping the nasal mucosa free of contaminants is a prerequisite for treating RS, yet there is currently no such treatment on the market. NESOSPRAY HE-G therefore acts as a multi-target and safe mechanical device for the treatment of RS, even in pregnant women, without resorting to unsafe chemical or biological drugs.

Conclusion

Treating RS with a stable and osmotic nasal poly-meric film is highly efficient and safe for the treat-ment of RS symptoms in all adult population, in-cluding during pregnancy. The efficacy is strong and fast, without any undesirable effects.

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