Evaluation of a novel natural drop for treatment of chronic rhinosinusitis without nasal polyps: a single blind randomized trial

Shima Vazifehkah, MD, PHD, Mohammad Reza Shams-Ardekani, PHD, Mohammad Kamalinejad, PHD, Seyed Mousa Saderhossein, MD, Hamed Hosseini, MD, Seyed Mohammad Shams, PHD, Shirin Abbassi, PHD, Sareh Eghtesad, MS, RD and Babak Saedi, MD

Background: The present study investigated the effectiveness of a Pimpinella anisum-based herbal medicine for treating chronic rhinosinusitis (CRS) without polyps in comparison to fluticasone nasal spray, in a single-blinded randomized trial.

Methods: Patients with CRS without nasal polyps were randomly assigned into 2 treatment groups: individuals in the first group (n = 26) received 2 drops of a P. anisum-based herbal medicine (Sinupim) in each nostril every 12 hours, while those in the second group (n = 22) received 2 puffs of fluticasone nasal spray in each nostril every 12 hours. Both groups used their designated treatments for 4 weeks. Patients were evaluated by the 22-item Sino-Nasal Outcome Test (SNOT-22) at the start of the trial and after the completion of their treatment.

Results: Although both treatments were effective in reducing patients’ symptoms, there were significantly better results in the Sinupim group based on the SNOT-22 evaluation. Mean changes in computed tomography (CT) scoring in Sinupim and fluticasone groups before and after treatment were 2.22 ± 2.94 and 0.76 ± 1.39, respectively, which was significant within both groups (p < 0.05). Post-nasal drip and nasal obstruction were more significantly improved in the Sinupim group.

Conclusion: A P. anisum-based herbal medicine may be an effective treatment for sinusitis without polyps. However, its wide acceptance needs further investigation. © 2016 ARS-AAOA, LLC.

Key Words: sinusitis; treatment; herbal medicine; Pimpinella anisum; SNOT-22; clinical trial


Chronic rhinosinusitis (CRS) is one of the most common chronic disorders with significant effects on patient’s quality of life. Its incidence is increasing each year without any known cause. Every year, about 18 to 22 million patients in the United States require clinical visits for CRS management and cost of CRS treatment is estimated to be more than 3 to 4.5 billion U.S. dollars.1-3

The cause of CRS is not well-known. The majority of cases are idiopathic and are characterized by the persistent inflammation of the nose and sinuses. Nasal endoscopy of some CRS patients shows polyps, which characterizes those patients as having “CRS with polyps.” CRS without nasal polyp, on the other hand, is a distinct disorder closely related to chronicity of unresolved acute infectious rhinosinusitis.4-6

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Antibiotics and intranasal steroids are the mainstays of CRS treatment. Evidence for support of these measures is limited and treatment results are not satisfactory. Extensive and long-term use of antibiotics may cause a surge in cost of treatment, a higher chance of drug interactions, side effects, antibiotic resistance, and a greater need for the use of new and expensive antibiotics. Concerns about long-term steroid usage still exist as well.2,4,6

Previous studies lack sufficient evidence on whether herbal medicine is effective for treating rhinosinusitis, especially in chronic cases. Nonetheless, there is some emerging proof, suggesting that certain herbal medicines, either alone or in combination with other types of treatment, may in fact be helpful in improving the symptoms of severe sinus infections.3

Interestingly, the use of other treatments including herbal drugs in the treatment of sinusitis is currently increasing. In 1 study about 32% of patients with chronic sinusitis used herbal medicine as a complementary treatment or used it alone.7,9 Also recent studies have stated the importance of first-line treatment of sinusitis symptoms with nonpharmacologic and natural medicines in order to limit and prevent improper use of antibiotics and subsequently prevent antibiotic resistance.10

However, few clinical trials have been performed to study the effect of herbal medicine in the treatment of CRS. In Iranian traditional medicine (ITM), several herbal products have been previously used for CRS treatment. Based on ITM texts, particularly the “Canon of Medicine,” Pimpinella anisum (P. anisum) is one of the medicinal herbs that can be effective in treating CRS. P. anisum belongs to the family Apiaceae and has been previously used in ITM for many different purposes. It has been used as an analgesic in headaches (caused by the common cold), an expectorant in coughs also associated with the cold, as well as a carminative, reducing bloating and flatulence. P. anisum has also been used as a diuretic, and has been known to improve breast milk production, halitosis reduction, and shortness of breath.11-16

In modern herbal medicine P. anisum has been reported as a remedy for catarrh of the upper respiratory tract. Commission E has approved the use of P. anisum for the inflammation of the lungs and throat, fever and common colds, inflammation of the mouth and throat, problems with indigestion and loss of appetite.17,18 Recent studies have shown many pharmacological effect of P. anisum, including its antibacterial, antifungal, antiviral, insecticidal, spasmyloytic, secretolytic, and antiepileptic properties, as well as its expectorant and bronchodilatory effects.19-21 Most of these effects are attributed to the presence of anethole (1.5-5%) in the P. anisum essential oil.22,23

The aim of this study is to compare the efficacy of a P. anisum-based drug with fluticasone nasal spray in patients with CRS without polyps.

This is the first randomized study to assess the P. anisum-based drug (Sinupim) on the treatment of CRS without nasal polyps.

Patients and methods
This was a single-blind, randomized study, including patients 18 to 75 years of age with a history of sinusitis for at least 3 months prior to study recruitment, and a diagnosis of CRS without polyps. Patients who were referred to the Rhinology Clinic of Imam Khomeini General Hospital (Tehran University of Medical Sciences, Tehran, Iran) presenting with 2 or more typical symptoms of CRS lasting for at least ≥12 weeks were assessed for eligibility.4 All patients underwent rigid nasal endoscopy. Presence of inflammation, nasal polyp, or mucopurulent discharge, especially in the middle meatus or the ethmoid area, was documented and those with active infection and polyps were excluded.

Diagnosis of CRS was confirmed with a paranasal sinus CT (PNS CT). Pretreatment PNS CT performed within 3 months of the clinical visit was considered as the “baseline” CT, and another was repeated after completion of the treatment and was considered the posttreatment PNS CT. The amount of sinus opacification was graded using the Lund-Mackay scoring system. Any mucosal changes in the sinuses or the ostiomeatal complex were documented. However, the minimum Lund-Mackay score was 4 in this series.

Anyone who had taken systemic or nasal antibiotics or nasal herbal medicine within 4 weeks of their visit at the clinic, as well as those who had taken oral corticosteroids within 30 days or topical corticosteroids within 15 days of their visit were excluded. Other exclusion criteria included those with a history of nasal and sinus surgery within the last 5 years, known hypersensitivity to the medication or excipients, those who were pregnant or breastfeeding, patients with cystic fibrosis, congenital mucociliary problems, immune deficiency, and systemic vasculitis, or any other severe concurrent illness. Anyone showing side effects during treatment was also excluded from the study after discontinuing the medication. Inclusion and exclusion criteria are shown in Table 1.

Ethical approval
This study was approved by the Institutional Review Board of Tehran University of Medical Sciences. Detailed information about the study was given to the participants and a written informed consent was obtained from each individual. Also, the trial was registered in the Iranian Registry of Clinical Trials with the number IRCT2014010516083N1.

Herbal medicinal product name
The herbal medicine used in this trial was an emulsion of the P. anisum seed and sweet almond oil; this product was named Sinupim. P. anisum seeds were purchased from the local market in Tehran. They were identified by staff botanist, and kept at the herbarium of the School of Pharmacy at Shahid Beheshti University of Medical Sciences, under the voucher number 8001.
Anisum seeds were first boiled in water for 20 minutes. Assuming the possibility of a 20% exclusion, 6 patients were not eligible; 66 patients had nasal polyposis, 28 patients were diagnosed with allergic rhinitis, 6 had recent antihistamine use, and 24 had been previously validated.

### Characteristics of the herbal product

*P. anisum* seeds were first boiled in water for 20 minutes. The amount of water was 4 times that of the *P. anisum* seeds. Subsequently, the aqueous extract was boiled in almond oil for 2 hours. After 24 hours, the isolated oil was used as the treatment medication, Sinupim. Sinupim was then packed in drop boxes and kept in the clinic’s refrigerator. Each drop box contained about 12 ml of Sinupim.

### Dosage regimen and quantitative description

In the treatment group, participants were instructed to use 2 drops of Sinupim in each nostril twice a day (morning and night) after normal saline irrigation. In the control group, a fluticasone propionate spray was used instead of Sinupim. Participants were instructed to use 2 puffs (total dose 200 μg) in each nostril, also twice per day (morning and night) after normal saline irrigation. Both groups used their designated treatments for 4 weeks.

### Outcomes

The efficacy of treatment was measured through changes in the 22-item Sino-Nasal Outcome Test (SNOT-22), which is a patient-reported test measuring outcomes in sinonasal disorders such as rhinosinusitis and nasal polyposis.24 An Iranian version of the questionnaire was used, which had been previously validated.25

### Randomization and blinding

A randomization sequence permuted block with a length of 4 was generated by computer. The clinicians were blinded to treatment allocation and, therefore, the researcher who enrolled and allocated the patients to groups was different from the clinicians who treated the patients. The blinding of patients was not possible, however, due to differences in shape, color, odor, and methods of using medicines.

The outcome evaluators were also blinded in assessment of CT scans, and filling of the SNOT-22 questionnaire.

### Statistical analysis

Means/standard deviations and frequency/percentages were measured for continuous and categorical variables, respectively. Independent and paired sample *t* test were used to compare differences between groups adjusted for baseline scores. Within-group treatment effects (before and after changes) were compared using paired sample *t* test. For all tests *p* < 0.05 was considered significant. All statistical analyses were performed using SPSS (version 19; IBM Corp., Armonk, NY).

A sample size of 22 in each group would achieve a 90% power to detect a difference of 10.0 between the null hypothesis (that both group means are 35.0) and the alternative hypothesis (that the mean of group 2 is 25.0) with an estimated group standard deviation of 10.0 and a significance level (alpha) of 0.05000 using a 2-sided 2-sample *t* test. Assuming the possibility of a 20% exclusion, 6 patients were added to each group. The final number for each group was 28.

### Results

From September 10, 2013, to March 23, 2015, a total of 171 patients referred to the rhinology clinic at Imam Khomeini General Hospital and were recruited for this study. Of those individuals, 115 patients were not eligible; 66 patients had nasal polyposis, 28 patients were diagnosed with allergic rhinitis, 6 had recent antihistamine use,
9 patients had acute infectious exacerbations, 5 recently took antibiotics, and 1 had an orbital tumor. The remaining 56 patients were randomized to receive Sinupim (n = 28) or fluticasone (n = 28) (see Fig. 1). Both groups were comparable for age, gender, and disease severity. Further exclusions were made in both groups after the start of treatments. In the Sinupim group, 2 patients were excluded since 1 started taking antibiotics and the other experienced intolerable headaches after 2 doses of the treatment. In the fluticasone group, 6 were excluded, 3 for antihistamine, 2 for antibiotic use, and 1 declined to participate. There were no significant differences between the SNOT-22 average of those excluded and the adherent patients. The average SNOT-22 scores for excluded patients from Sinupim and fluticasone groups were 42.5 and 43.8, respectively.

Twenty-six patients from the Sinupim group and 22 from the fluticasone group who completed the trials were included in the final analysis. Demographics and baseline rhinologic information of both groups’ participants are shown in Tables 1 and 2, respectively. The effects of treatment are reported as “within group treatment effects” in Table 3 and “between group treatment effects” in Table 4. There were 15 male and 11 female patients in the Sinupim group and 14 males and 8 females in the fluticasone group. The mean age (range) in the Sinupim and fluticasone groups was 41.00 years (range, 23–68 years), and 37.63 years (range, 18–66, years), respectively. Neither the demographics, nor the baseline rhinologic information (including SNOT-22 symptoms scoring and Lund-Mackay CT scan scoring systems) were significantly different in the 2 groups.

Treatment outcomes

At the end of treatment, as presented in Table 3, the mean change in SNOT-22 was highly significant within both the Sinupim group (20.80 ± 16.24; 95% CI, 14.24 to 27.36; p value < 7.6 E−7) and the fluticasone group (10.36 ± 10.30; 95% CI, 14.24 to 27.36; p value < 1.1 E−4).

Comparisons between the 2 groups were also made using before and after treatment scores (Table 4, rows 1 and 2). Differences in the mean SNOT-22 scores were significant (p < 0.012) indicating a greater change in the Sinupim group. In addition, the mean improvement in CT scan scores was significantly greater in the Sinupim group in comparison to the fluticasone group (p < 0.06).

Further between-group evaluation of the effects of treatment on the rhinological symptoms subscale of SNOT-20 (need to blow nose, sneezing, postnasal discharge, runny nose) was performed, to more specifically demonstrate the therapeutic role of Sinupim and fluticasone (Table 4, rows 3 to 6). This evaluation showed that the mean changes in rhinologic symptoms improved more in the Sinupim group (p = 0.007)
TABLE 2. Baseline characteristics of 55 study participants with clinically diagnosis of CRS without polyps

<table>
<thead>
<tr>
<th></th>
<th>Sinupim group (n = 26)</th>
<th>Fluticasone group (n = 22)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>41.00 ± 12.36</td>
<td>37.63 ± 12.80</td>
<td>0.931</td>
</tr>
<tr>
<td>Sex (M/F), n (%)</td>
<td>15/11 (59.6/42.3)</td>
<td>14/8 (63.63/36.36)</td>
<td>0.86</td>
</tr>
<tr>
<td>Married/unmarried, n (%)</td>
<td>23/2 (92/8)</td>
<td>19/3 (86.3/13.6)</td>
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<tr>
<td>Educational level, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ High school</td>
<td>11 (42.3)</td>
<td>8 (36.36)</td>
<td></td>
</tr>
<tr>
<td>≤ Bachelor’s degree</td>
<td>11 (42.3)</td>
<td>13 (59)</td>
<td></td>
</tr>
<tr>
<td>Postgraduate</td>
<td>4 (15.3)</td>
<td>1 (4.5)</td>
<td></td>
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<tr>
<td>Drug history, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic</td>
<td>14 (93.3)</td>
<td>18 (94.7)</td>
<td></td>
</tr>
<tr>
<td>Antihistamine</td>
<td>8 (53.3)</td>
<td>11 (57.8)</td>
<td></td>
</tr>
<tr>
<td>Nasal steroid</td>
<td>8 (53.3)</td>
<td>13 (68.4)</td>
<td></td>
</tr>
<tr>
<td>Herbal medicine</td>
<td>3 (20)</td>
<td>2 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Nasal irrigation</td>
<td>9 (60)</td>
<td>10 (55.55)</td>
<td></td>
</tr>
<tr>
<td>GER, n (%)</td>
<td>4 (23.5)</td>
<td>8 (53.3)</td>
<td></td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>8 (30.7)</td>
<td>4 (18.18)</td>
<td></td>
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<tr>
<td>SNOT-22 score, mean ± SD</td>
<td>44.92 ± 20.87</td>
<td>44.68 ± 15.17</td>
<td>0.96</td>
</tr>
<tr>
<td>CT scan score, mean ± SD</td>
<td>8.92 ± 6.26</td>
<td>8.68 ± 6.70</td>
<td>0.90</td>
</tr>
<tr>
<td>Symptoms duration (months), mean ± SD</td>
<td>5.42 ± 3.07</td>
<td>5.77 ± 3.30</td>
<td>0.70</td>
</tr>
</tbody>
</table>

*a Mean of the 22 sinusitis symptoms (0 = no problem, 1 = very mild problem, 2 = mild or slight problem, 3 = moderate problem, 4 = severe problem, 5 = problem as bad as it can be).

*b The CT scan score was based on Lund-Mackey scoring (maximum of 24).

CRS = chronic rhinosinusitis; CT = computed tomography; GER = gastroesophageal reflux; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test.

TABLE 3. The within group treatment effect*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Score</th>
<th>Before treatment (mean ± SD)</th>
<th>After treatment (mean ± SD)</th>
<th>(Before − after) (mean ± SD)</th>
<th>95% CI of the difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone (n = 22)</td>
<td>SNOT-22</td>
<td>44.68 ± 14.17</td>
<td>34.31 ± 15.01</td>
<td>10.36 ± 10.30</td>
<td>[5.79–14.90]</td>
<td>1.1 E−4</td>
</tr>
<tr>
<td>Sinupim (n = 26)</td>
<td>CT</td>
<td>10.04 ± 5.81</td>
<td>7.81 ± 5.68</td>
<td>2.22 ± 2.94</td>
<td>[0.92–3.53]</td>
<td>0.002</td>
</tr>
<tr>
<td>Fluticasone (n = 22)</td>
<td>CT</td>
<td>10.42 ± 5.92</td>
<td>9.64 ± 6.08</td>
<td>0.76 ± 1.39</td>
<td>[0.048–1.48]</td>
<td>0.038</td>
</tr>
</tbody>
</table>

*a Paired samples t test.

CI = confidence interval; CT = computed tomography; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test.

Safety and tolerability

Sinupim was well tolerated by patients. There were no serious adverse effects in either group. The most common problems reported were increased discharge (n = 7), nausea (n = 3), and headache (n = 1) in the Sinupim group, and nasal dryness (n = 3), bloody discharge (n = 1), and hoarseness (n = 1) in the fluticasone group.

Discussion

Based on the Iranian traditional medicine, *P. anisum* is 1 of the medicinal herbs that can affect CRS symptoms. The antibacterial, antifungal, antiviral, analgesic, and anti-inflammatory properties of *P. anisum* have been shown in previous studies.11–18

Current evidence demonstrates that nasal corticosteroids are beneficial in controlling CRS symptoms, yet there is...
little evidence on their adverse effects. In this study, the effects of a *P. anisum*–based herbal medicine were compared with those of a fluticasone nasal spray, in the treatment of CRS without polyps.

SNOT-22 is a reliable and valid patient-reported questionnaire that measures subjective outcomes of inflammatory sinonasal disorders. It covers rhinologic, ear, facial, sleep, psychological, and other factors that may affect patient outcomes. In this study, an Iranian version of SNOT-22 was used, which had previously been shown to be reliable and valid. Both SNOT-22 and SNOT-20 rhinologic symptoms subscale, including need to blow nose, sneezing, runny nose, postnasal discharge, and thick nasal discharge, were examined. Also other subscales of SNOT-20 such as ear and facial symptoms, sleep function, and psychologic factors were examined. The SNOT-20 subscales were used to show the treatment outcomes more specifically. The pretreatment SNOT-22 scores in both Sinupim and fluticasone groups were similar to those reported by another study in CRS patients in the United Kingdom (44.1 ± 20.4).

The mean change in SNOT-22 scores in the Sinupim and fluticasone groups were 20.80 ± 16.24 and 10.36 ± 10.30, respectively (p = 0.012). It has been shown that a reduction of at least 9 points in the SNOT-22 score implies a real benefit perceived by the patients. Topical steroids, when compared to placebo, have improved sinonasal symptom scores in patients with CRS and more patients responded to them. The significant reductions in SNOT-22 scores indicate that both groups in this study benefited from the medications they received.

The paranasal sinus CT scan is an objective tool that measures the amount of inflamed mucosa in CRS. The Lund-Mackay score is the most widely accepted system for classifying CT scans in CRS but it does not correlate well with SNOT-22 scores. Also it cannot specify the level of grade I inflammation, which could be anywhere between 1% and 99% opacification. Therefore, it can be concluded that adequate detection of mild to moderate changes in the volume of inflamed sinus mucosa is not possible. Furthermore, the Lund-Mackay scoring system does not take into consideration individual sinus drainage areas such as the frontal and maxillary sinuses.

In this study, pretreatment Lund-Mackay paranasal sinus CT scores were 10.04 ± 5.81 and 10.42 ± 5.92 in Sinupim and fluticasone groups, respectively. In the U.K. study, the average CT scores in those who had CRS without polyps (n = 848) was 7.0 ± 4.7. The comparison of these scores shows that the participants of the present study had a more severe inflammatory sinus disease than those in the United Kingdom.

Mean changes in Lund-Mackay CT scan scores in Sinupim and fluticasone groups before and after treatment were 2.22 ± 2.94 and 0.76 ± 1.39, respectively. Comparison of the 2 groups showed better results in patients who received Sinupim (p = 0.06). Possible reasons for which the mean changes in CT scores between the 2 groups were not significant may include the short duration of treatment and lack of precision in the scoring system. Also, since the pathophysiology of CRS is not clearly understood, it is usually expected to have persistent mucosal inflammation in spite of treatment.

The other important diagnostic tool in sinusitis was nasal endoscopy, which was used in patients’ initial evaluation. However, as an outcome measure tool, it may be more effective in nasal polyposis.

Focusing on the major rhinologic symptom scores of the SNOT-20 revealed that most of these symptoms significantly improved in both groups. Rhinologic symptoms and psychologic issues were more significantly improved in the Sinupim group. These 2 complaints are highly specific in CRS and are major complaints among patients seeking relief. Although intranasal steroids are the main medication used for relief of nasal obstruction in CRS, this study showed that Sinupim may also have promising effects on this symptom.

Limitations of this study include a small sample size and a short treatment course. Most of the patient who were diagnosed with CRS in the rhinology clinic had polyps or suppuration and thus were excluded from this study. Also most of patients were reluctant to continue using Sinupim and looked for more definitive treatments, especially surgery.

Our result showed that although both groups had improvements after 4 weeks of treatment, the Sinupim group had significantly better outcomes than the group treated with fluticasone. Few participants had some side effects, the most important of which was headaches. Further investigation should be done in this regard before its widespread usage.

To our knowledge this was the first report on the effectiveness of a *P. anisum*–based herbal medicine in chronic sinusitis. The positive results of this study warrants further investigation in this field.

<table>
<thead>
<tr>
<th>TABLE 4. The between-group treatment effect*</th>
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<tr>
<td>Pretreatment and posttreatment changes</td>
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<tr>
<td>------------------------------------------</td>
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<tr>
<td>SNOT-22 change</td>
</tr>
<tr>
<td>CT scan change</td>
</tr>
<tr>
<td>Rhinological factors</td>
</tr>
<tr>
<td>Ear and facial symptoms</td>
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<tr>
<td>Sleep function</td>
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<tr>
<td>Psychological issue</td>
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</table>

*Independent samples t test. CT = computed tomography; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test.
A novel natural drop for treatment of CRS

Conclusion

P. anisum–based herbal product can be an effective medication in the treatment of chronic sinusitis without polyps.

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