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Effect of *Myrtus communis* L. Syrup on Chronic Rhinosinusitis: A Randomized Double-Blind, Placebo-Controlled Pilot Study

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Abstract

Background: According to the Iranian Traditional Medicine (ITM) resources, myrtle (*Myrtus communis* L.) resolves swelling, wounds and injuries; its wound exsiccation capability and tissue enforcement properties may be helpful in the treatment of the rhinosinusitis.

Objectives: The objective of the current trial was to assess the effects of *Myrtus communis* aqueous extract in the treatment of chronic rhinosinusitis.

Methods: A total of 38 patients referring to the Masih Daneshvari Hospital (Tehran, Iran) for the treatment of chronic rhinosinusitis during the year 2016 were recruited for a double-blinded randomized placebo-controlled trial. They were randomly allocated in 2 groups: 22 patients were in the treatment group and 16 patients in the placebo group. Recruitment was based on the European position paper on rhinosinusitis (EPOS). Patients' data, including demographic information, SNOT22 questionnaire scores, and visual analog scale (VAS), were gathered and recorded by an otolaryngologist. Patients were investigated with a CT scan of the paranasal sinuses at the beginning of the study.

Results: A total of 13 patients (59.1%) in the treatment group were female and 7 in the placebo group (43.7%). The median age of patients in the treatment group was 38.86 (18 - 68) and in the placebo group 39.93 (22 - 75) years. Data analysis revealed that symptoms improved in the treatment group after treatment in most parameters, according to the SNOT- 22 parameters. However, most of these improvements, such as reduced concentration (1.81 ± 2.01 vs. 0.73 ± 1.32 in control vs. treatment group, respectively; $P = 0.055$), frustrated/restless/irritable (1.56 ± 1.97 vs. 0.55 ± 1.1 in control and treatment groups, respectively; $P = 0.113$), as well as ear pain ($P = 0.121$), did not demonstrate a statistical significance. There was a significant improvement in symptom number 18 (reduced productivity) in the SNOT- 22 questionnaire (1.69 ± 1.92 vs. 0.77 ± 1.23 in control vs. treatment group, respectively; $P = 0.041$).

Conclusions: According to the present study findings, *Myrtus communis* L. syrup can be safely administered in patients with chronic rhinosinusitis and is effective in improving the outcomes of the disease.

1. Background

Current therapies, topical or systemic, have effectively helped with the treatment of the chronic rhinosinusitis (CRS); however, there is currently no standard treatment for the condition (1).

Treatments include antibiotics, corticosteroids, antihistamine, nasal lavage, decongestants, immunotherapy, and surgery. It has been estimated that in the year 2014, the costs for the treatment of patients suffering from rhinosinusitis was $6.9 to $9.9 billion. The endoscopic operation costs around $1547 to $2,00 for each patient (2). Secondary conditions may arise after the disease, which mostly include 2 categories: 1) orbital ocular (60 - 75%) and 2) intracranial complications (15 - 20%) (3). The disease has infectious and noninfectious cases. Noninfectious cases include allergy, and environmental factors including air pollution and physiologic causes or age-related conditions (e.g. vasomotor or hormonal reasons. Infectious causes include fungal, bacterial, viral and other infectious agents (4).

Myrtus communis, also known as the common myrtle, is a species of a flowering plant in the myrtle family Myrtaceae. It is an evergreen shrub native to Iran, other Mid-

dle East countries, south Asia, and Europe (5, 6). Myrtle has known anti-inflammatory (6, 7), antibacterial (8), antiviral (9, 10), and antifungal (8, 11, 12) properties, which makes it a good candidate for the treatment of infectious and inflammatory diseases. According to the ITM resources, myrtle resolves swelling, wounds, and injuries (13); its wound exsiccation capability and tissue enforcement properties may be helpful in the treatment of the rhinosinusitis (14). Since 1, 8-cineole is the main pharmaceutically active constituent of this plant (15) and it has been proved to be effective in the treatment of the sinusitis (16). We stipulated that oral syrup of *Myrtus communis* is effective in the treatment of the condition. In the current study we investigated the effects of syrup prepared from the *Myrtus communis* aqueous extract on the outcomes of rhinosinusitis in human subjects.

2. Methods

2.1. Patients and Study Design

A double-blinded randomized placebo-controlled trial was conducted for the assessment of the effects of *Myrtus communis* aqueous extract syrup in the treatment of chronic rhinosinusitis. Patients referring to the Masih Daneshvari Hospital (Tehran, Iran) for the treatment of chronic rhinosinusitis during the year 2016 were recruited for a double-blinded randomized placebo-controlled trial. They were inspected for eligibility to participate in the current study. The study was approved by the Ethics Committee of the Shahid Sadoughi University of Medical Sciences (reference number: IR.SSU.REC.1394.148). Furthermore, researchers followed the Helsinki declaration for medical research including human subjects. An informed written consent form was signed by each participant. The study was registered at the Iranian Registry of Clinical Trials (IRCT), available at http://irct.ir/, with registration number of "IRCT2016020926465N1". The physician assessing the outcome as well as the patients were unaware of the allocation sequence for blinding. Patients were recruited according to the European position paper on rhinosinusitis (EPOS) (17). Since we did not have an estimate of the main outcome measures, we ran this pilot study with available samples to get an estimate of the measures. The main inclusion criteria included nasal congestion, nasal discharge (anterior or posterior), pain or pressure in the face, and reduction or loss of smell for more than 12 weeks appeared in the last 12 months. Having at least 2 of the aforementioned symptoms or 1 of the major criterion plus 2 of the minor criteria (including dental pain, cough, pain, pressure or fullness in ears, fatigue, headaches or bad breath) and in case of doubt diagnostic, diagnostic endoscopy of the sinuses (based on the presence or absence of draining sinuses and thickness), was set as a diagnostic criteria for chronic sinusitis. The exclusion criteria included the following: allergy or sensitivity to the medicines, previous sinus surgical operation, systemic administration of corticosteroids in the last 3 months, psychological disturbances interfering with the patients cooperation, pregnancy or lactation in women, orbital or neurological complications of the sinusitis, recent (1 week) use of antibiotics, and Lund Mackay score of 0 (no apparent pacification of the paranasal sinuses in CT scans).

Patients who met the inclusion criteria were randomly assigned in 2 groups. Randomization was performed by the simple randomization method using the MS Excel software (Microsoft Corporation, Washington, US), as described previously (18). Briefly, each patient was assigned a code. Codes were entered in a spreadsheet file and each received a random value from between 0 to 1. Patients received a placebo if the corresponding random value was below 0.5 and Myrtus syrup if the corresponding random value was equal or more than 0.5. Patients did not stop taking the normal medications for the treatment of their diseases for ethical concerns. The control group received regular treatment for their condition including 2 puffs a day of corticosteroid spray, twice daily nasal irrigation with normal saline in the morning and the evening, as well as antibiotic therapy in case of purulent sinusitis. The intervention group received the regular treatment plus oral dosages of *Myrtus communis* extract for 1 month.

2.2. Plant Material

Dried myrtle berries were prepared from the local market, Tehran, Iran. Material was authenticated by Mohammad Kamalinejad. A voucher specimen of the plant has been deposited in Shahid Beheshti University of Medical Sciences' Herbarium, School of Pharmacy, under the voucher No 8044-SBMU.

2.3. Syrup Preparation

In Iranian Traditional Medicine (ITM) texts decoction is described in "Qarabadin" (Ghayeni, Qarabadin-e-Salehi, 1765 AD; Aghili, Qarabadin-e-Kabir, 1781 AD) (19, 20). We used a modified version of the method adapted to modern instrumentation to prepare the extract. Briefly, the aqueous extract of fruit of the plant *Myrtus communis* L. was prepared as follows: 100 grams of the fruit was boiled in 1 liter of water for 30 minutes; then, extract was cooled into room temperature and filtered by standard filter papers. Extract was dried in an incubator. A total of 50 grams of dried extract powder was obtained for 500 grams of fruit dry weight. 3% syrup was prepared with 50% sugar. The syrup

was prepared under hygienic conditions and properly labeled. The placebo was prepared with 50% sugar, without the active ingredients, including approved color additives. It looked the same as the myrtle syrup. The drug and the placebo were stored in 300 ml syrup glass bottles and used for the treatment of the patients. The drug was prescribed as 10 milliliters twice daily (5 milliliter each morning and evening) oral doses.

2.4. Data Collection and Main Outcome Measures

Patients' data, including demographic information, SNOT22 questionnaire, and VAS (21-23) scores were gathered and recorded by an otolaryngologist. All examinations and assessments were performed by 1 otolaryngologist. Patients were investigated with a CT scan of the paranasal sinuses at the beginning of the study.

The myrtle syrup and placebo were identical in the physical form, packaging, as well as labeling and they were divided in groups G, F, R, L, M, and S. Bottles labeled with the first 3 (G, F and R) letters contained myrtle syrup and other bottles contained placebo. The physician prescribed syrups to the patients according to the label numbers. Physician, as prescribers and outcome assessors of the myrtle syrup or placebo, were blinded for the treatments. Only the pharmacist was aware of the allocation groups.

2.5. Statistical Analysis

Continuous data with normal distribution were presented as mean ± standard deviation. Continuous variables with non-normal distribution were presented as median (interquartile range; IQR). Nominal data were presented as frequency and frequency percent. Data analysis was performed using SPSS v18 (IBM, New York, United states). Data analysis was performed with the power of 0.8 and statistical significance level of 0.05. Covariance analysis was used for testing the differences between SNOT22 test scores between groups after treatment. Unpaired t-test was used for between group comparisons where continuous data follows the normal distribution. In case of non-normal distribution, Mann-Whitney U test was used for between group comparisons. Categorical data was analyzed using the chi-square test.

3. Results

For studying the effects of daily oral *Myrtus communis* L. syrup on the symptoms of rhinosinusitis in a double-blinded placebo-controlled trial, 123 patients were assessed for eligibility for participation in the study. A total of 80 patients were excluded from the study due to following reasons: 77 patients did not meet the criteria for inclusion in the study, 1 declined to participate, and 2 prefer to receive surgical treatment. A total of 43 patients were randomly allocated in 2 groups: 25 patients in the treatment group and 18 patients to the placebo group (Consort diagram in Figure 1). Finally, 22 patients in the treatment and 16 patients in the placebo group finished the study and their data was included in the analysis. Thirteen out of 22 patients (59.09%) in the treatment group and 7 out of 16 patients in the placebo group (43.7%) were females. The mean age of patients in the treatment group was 38.86 (18 - 68) and in the placebo group 39.93 (22 - 75) years. Median symptom time was 58.5 (3 - 204) months in placebo group and 69.69 (3 - 360) months in the myrtle syrup groups. The Lund-Mackay score before treatment was 7.45 (3 - 18) in the treatment group and 6.62 (1 - 18) in the placebo group.

According to the results, the total symptoms score significantly improved in both groups over time ($P < 0.001$), however, the overall improvement was not significantly different after treatment between 2 groups 24.43 in intervention vs. 24.04 in the control group $P = 0.19$). Nonetheless, analysis revealed that some symptoms improved in the treatment group after treatment in many parameters according to the SNOT- 22 tool. Table 2 demonstrates the mean values of pre- and post-treatment SNOT- 22 items scores, and probability values. The items that showed improvement after treatment included nasal obstruction, loss of smell or taste, cough, post nasal discharge, thick nasal discharge, ear fullness, facial pain/pressure, difficulty in falling asleep, waking up at night, lack of good night's sleep, wake up tired, reduced productivity, and embarrassed. However, most of these improvements such as reduced concentration ($P = 0.055$), frustrated/restless/irritable ($P = 0.113$), and ear pain ($P = 0.121$), did not demonstrate statistical significance. There was a significant improvement in the symptom number 18 (reduced productivity) in the SNOT- 22 questionnaire ($P = 0.041$).

Table 1. Demographic Information Related to Patients in Groups Receiving Myrtus and Placebo Respectively

	Myrtle Syrup	Placebo	P-Value
Age (years)	38.86 (18-68)	39.93 (22 - 75)	0.453
Sex (female %)	13/22 (59.1%)	7/16 (43.7%)	0.512
Education (years)	10.13 ± 6.15	12.27 ± 3.45	0.179
Lund Mackay score	7.45 (3 - 18)	6.62 (1 - 18)	0.231

Table 2. Scores of 22 Items of the SNOT-22 Questionnaire in Study Groups Before and After Treatment

Group	Mean ± SD Before Treatment		Mean ± SD After Treatment		F	P-Value
	Control	Intervention	Control	Intervention		
1. Need to blow nose	3 ± 1.79	1.82 ± 2.11	1.88 ± 1.86	0.96 ± 1.4	0.865	0.359
2. Sneezing	2.44 ± 2.16	2.0 ± 2.05	1.0 ± 1.37	0.41 ± 1.0	1.986	0.168
3. Runny nose	3 ± 1.75	2.36 ± 1.89	0.69 ± 1.08	0.5 ± 1.1	0.146	0.704
4. Nasal obstruction	1.94 ± 1.69	0.86 ± 1.28	0.69 ± 1.2	0.5 ± 1.23	0.088	0.769
5. Loss of smell or taste	3.13 ± 1.63	2.36 ± 1.97	1.94 ± 1.53	1.05 ± 1.6	2.159	0.151
6. Cough	1.69 ± 1.89	1.96 ± 1.96	1.06 ± 1.61	0.77 ± 1.34	1.052	0.312
7. Post-nasal discharge	1.75 ± 1.92	1.09 ± 1.48	1.5 ± 1.71	0.73 ± 1.28	1.043	0.314
8. Thick nasal discharge	1.31 ± 1.85	0.91 ± 1.41	0.69 ± 1.2	0.23 ± 0.87	1.259	0.269
9. Ear fullness	1.31 ± 1.85	0.73 ± 1.35	0.63 ± 1.15	0.77 ± 1.37	0.673	0.418
10. Dizziness	2.5 ± 1.83	1.18 ± 1.68	0.88 ± 1.46	0.41 ± 0.86	1.279	0.266
11. Ear pain	2.25 ± 2.11	2.64 ± 2.47	1.31 ± 1.99	0.73 ± 1.42	2.525	0.121
12. Facial pain/pressure	2.75 ± 1.57	2.18 ± 2.02	1.38 ± 1.46	0.73 ± 1.42	1.365	0.251
13. Difficulty falling asleep	2.13 ± 2.09	1.73 ± 2.05	1.06 ± 1.44	0.86 ± 1.49	0.042	0.840
14. Waking up at night	3.31 ± 1.78	2.0 ± 2.0	1.75 ± 1.92	1.23 ± 1.45	0.000	0.983
15. Lack of a good night's sleep	3.0 ± 1.83	2.14 ± 1.78	1.88 ± 1.96	1.27 ± 1.49	0.241	0.626
16. Waking up tired	2.13 ± 2.25	1.73 ± 2.0	1.31 ± 1.54	0.91 ± 1.34	0.414	0.524
17. Fatigue	2.5 ± 2.28	1.41 ± 1.79	1.31 ± 1.74	0.77 ± 1.23	0.019	0.891
18. Reduced productivity	2.25 ± 2.08	2.23 ± 1.85	1.69 ± 1.92	0.77 ± 1.23	4.505	0.041
19. Reduced concentration	2.5 ± 1.93	2.09 ± 2.0	1.81 ± 2.01	0.73 ± 1.32	3.954	0.055
20. Frustrated/restless/irritable	2.13 ± 2.34	1.27 ± 1.88	1.56 ± 1.97	0.55 ± 1.1	2.636	0.113
21. Sad	2.75 ± 1.84	3 ± 2.12	1.69 ± 1.82	1.68 ± 1.73	0.140	0.710
22. Embarrassed	4.19 ± 1.33	4.46 ± 0.91	1.81 ± 1.6	1.55 ± 1.79	0.333	0.568

Data is presented as mean ± standard deviation (SD)

4. Discussion

We conducted the current study to inspect the effects of daily oral *Myrtus communis* L. syrup on the symptoms of rhinosinusitis in a double-blinded placebo-controlled trial. A total of 43 patients were randomly allocated in 2 groups, namely treatment with *Myrtus communis* L. and placebo. They were studied for 1 month and the symptoms were measured and recorded carefully. To refrain from patients' withdrawal from standard treatment due to ethical concerns we administered the *Myrtus communis* L. syrup as a supplement to the standard therapy. It appeared that simultaneous use of standard therapy has masked the effects of the myrtle syrup; therefore, effectiveness of myrtle syrup alone, as a treatment, needs to be assessed. The results showed statistically significant improvement in 1 item (reduced productivity) and improvement in many other items, which lacked clinical significance. We did not observe clinical adverse effects, which could be attributed to the use of the myrtle syrup. To date, the safety of the products from this traditional herbal medicine has been reported in various studies (24-27). Babaee et al., used a paste containing *Myrtus communis* L. (Myrtle) in the treatment of recurrent aphthous stomatitis (24). Their study demonstrated that 4 times a day for 6 days oral topical application of the paste containing myrtle extract effectively improves outcomes in recurrent aphthous stomatitis without any side effects. Zohalinezhad et al., reported the safety and efficacy of the myrtle berries freeze-dried aqueous extract, 1000 mg/d for the treatment of gastroesophageal reflux disease (26). According to a report by Ghadami Yazdi et al., its topical application on skin is safe and effective for the treatment of warts (25). The present study provides evidence on the safety and efficacy of the oral use of myrtle aqueous extract syrup for the treatment

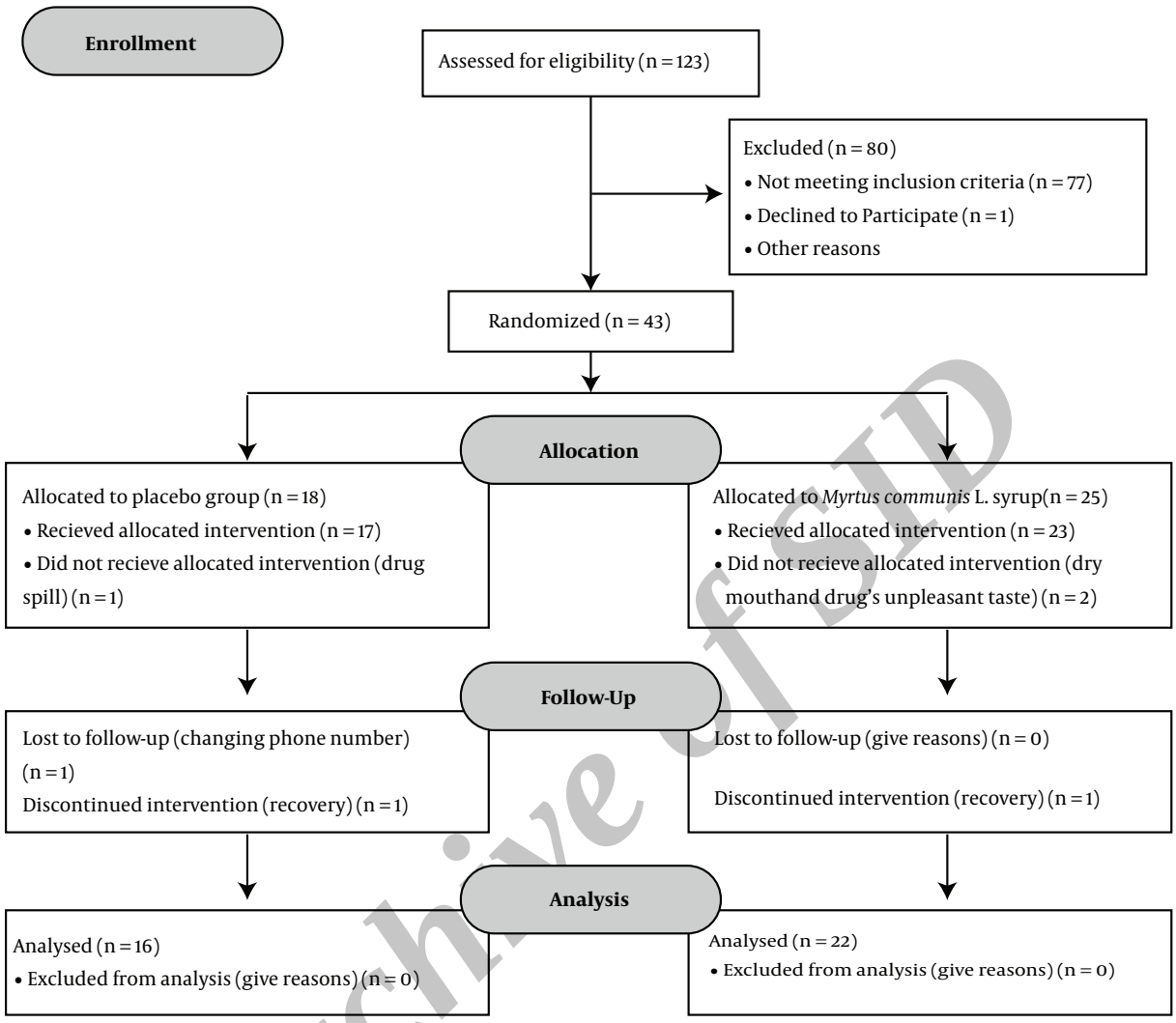
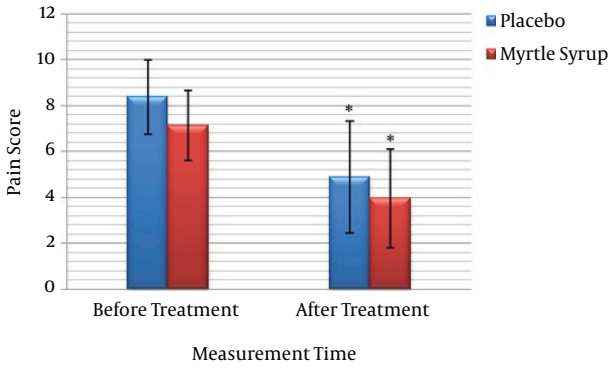


Figure 1. Consort Flow Diagram Demonstrates the Study Design and Timeline

of rhinosinusitis. Rhinosinusitis is a disease with infectious and inflammatory pathogenesis similar to the conditions mentioned above. Since myrtle has known anti-inflammatory, antibacterial, antifungal and antiviral effects it can improve the outcomes of rhinosinusitis (15, 28-32). The myrtle syrup appears to be tolerable and safe for the patients with rhinosinusitis. No significant side effects were observed with the use of the syrup. Two patients withdrew from study; 1 due to the dry mouth and the other because of the unpleasant taste of the drug. Drug was proved to be effective in the treatment of the rhinosinusitis. It significantly improved the productivity of the patients as assessed by SNOT-22 questionnaire method. It also had beneficial effects on most of the parameters of the disease; however, the effects were not statistically significant. Therefore, conducting a study with increased sample size is required. Sudhoff et al., reported that 1.8-Cineol effectively inhibits the mucus production in in vitro models of rhinosinusitis (33). 1.8-Cineol is 1 of the important *Myrtus communis* active pharmaceutical ingredients and has antibacterial activity (15). 1.8-cineole has proven anti-inflammatory and anti-microbial activity (34, 35). Kehrl et al., demonstrated the safety and efficacy of this compound in the treatment of rhinosinusitis in a randomized controlled trial. Their study reported no side effects for this compound when 2 100-mg capsules of cineole was administered 3 times daily (16). Their study suggests that timely intervention in patients with rhinosinusitis, before indi-

Figure 2. Visual Analog Score for Measurement of Pain Before and After Treatment With Myrtle Syrup in Patients With Rhinosinusitis



Data presentation is as mean ± SD. * P-value less than 0.05 compare to the measurement before treatment in the same group.

cation of treatment with antibiotics, could effectively improve the outcome and treat the disease (16). Myrtle syrup can contain higher doses of this product and according to the current study it could be safely administered in patients with rhinosinusitis. This finding paves the way for using higher doses of the 1.8-cineole through prescribing myrtle syrup.

The findings of the current study are consistent with the previous evidence. For the first time, it provides proof of the safety and efficacy of myrtle derivatives and extracts for human use and as an oral medication for the treatment of rhinosinusitis. One limitation of the current study is the small sample size, since it is a pilot study. Since we were not confident about the efficacy of the syrup, we had to use myrtle syrup as an adjuvant therapy to prevent observing the patient's right to access the standard therapy. Therefore, it is very difficult for estimating the efficacy of the drug and its effect may be masked with the standard therapy. We suggest studies with larger sample sizes to be conducted in patients before indication of the other medications prescribed for rhinosinusitis.

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