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Original Article

Treatment of rhinosinusitis and dry eye with an antibacterial honey nasal spray

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ABSTRACT

Aim: Chronic rhinosinusitis is an inflammatory disease of the nasal mucosa often occurring concurrently with dry eye. The aim was to assess the effects of Manuka (*Leptospermum spp.*) antibacterial honey nasal spray (Melcare® Manuka+ ™ Nasal Spray, Melcare, Australia) and eye drops (Optimel Manuka+ Dry Eye Drops, Melcare, Australia) on both conditions. The safety of and adherence to these treatments were also evaluated. **Methods:** Twenty-seven participants, aged 50 to 77 years, with chronic rhinosinusitis and dry eye symptoms were recruited and randomised to two treatment groups; 22 completed the study. One group used the Manuka Nasal Spray (n=10) and the other the Manuka Nasal Spray plus Manuka Dry Eye Drops (n=12); treatments were used twice daily for 4 weeks. Before and after treatments symptoms were surveyed (SNOT-20, ODSI) and ocular surface assessed (bulbar and limbal conjunctival redness, non-invasive and fluorescein tear break up times, tear secretion, ocular surface staining). Participants completed a daily log of their usage of treatments and any issues experienced. **Results:** Both treatment groups showed significant improvements in nasal symptoms, and decreased surface staining. Participants using the Manuka+ Dry Eye Drops also had a reduction in their dry eye symptoms. There was no significant difference between the effects of the two treatments on ocular surface assessments. No adverse responses were reported to either treatment. **Conclusions:** The Manuka+ Nasal Spray is effective in improving symptoms of chronic rhinosinusitis over a 4 week period, but must be used in conjunction with the Manuka+ Dry Eye Drops to improve concurrent dry eye symptoms.

KEY WORDS: Antibacterial honey; Dry eye; Leptospermum species; Manuka honey eye drop; Rhinosinusitis

INTRODUCTION

Dry, red, sore, irritated eyes affect one in three adults [1]. Dry eye disease adversely affects our ability to see clearly, read comfortably, work productively and interact socially [2]. At its' worst, dry eye disease adversely affects our quality of life and can lead to infection, scarring and permanent vision loss [3]. Dry eye conditions are often poorly responsive to conventional lubricant eye drops and eye lid hygiene treatments [4].

Between the ocular (eye) surface and the nose, the nasolacrimal apparatus is a direct physical connection of the ocular surface to the nasal mucosa (mucosa lining). The majority (75-85%) of the tears drain from the eye surface into the nasolacrimal sac and the nasolacrimal duct and empty into the nose. Additionally the eye and the nose are interconnected connected by neural (nerve) and venous (blood vessel) systems [5].

Chronic rhinosinusitis (CRS) is a prevalent and debilitating disease, comprising a spectrum of inflammatory and infectious diseases that concurrently affect both the nose and paranasal sinuses for longer than three months [6]. Like dry eye disease, CRS significantly impacts quality of life, and, not only causes significant physical symptoms, but also results in substantial functional and emotional impairment [7]. The prevalence of CRS is approximately 10% to 15% [6] with dry eye symptoms reported by nearly 70% of CRS sufferers [8]. Both CRS and dry eye involve inflammation of mucosal (mucous producing) surface tissue which may have a common immune mediated cause [6, 9]. Also, a lack of the aqueous component in the tears in dry eye disease and associated lack of antimicrobial proteins in the tears and increase in pro-inflammatory factors in dry eye might contribute to poor sinus drainage and bacterial overgrowth [8].

Treatment of CRS is primarily focused on reducing mucosal inflammation, removing bacterial infection/colonization, and improving sino-nasal function. Medical therapies used include nasal saline irrigation and saline sprays, nasal steroids, oral antibiotics and functional endoscopic sinus surgery in individuals with CRS non-responsive to medical treatment [10]. Some patients with CRS fail to respond to either conventional medical or surgical intervention [6,10], and hence alternative therapies are sought by patients and practitioners [10].

There is some evidence to suggest that honey, an anti-microbial and anti-inflammatory agent may be beneficial as a safe, low-priced adjuvant therapy, to reduce inflammation and foster mucosal healing in patients suffering from chronic rhinosinusitis [11]. Honey does not have the side effects of chronic nasal steroid use, such as increased intraocular pressure and cataract formation [12] nor the resistance issues associated with repeated antibiotic dosing [13].

In vitro evidence has indicated that Manuka honey is an effective agent for preventing Staphylococcal and Pseudomonas biofilm formation [14,15] and does not cause epithelial injury, inflammation or morphological changes to the tissue [16]. However, Manuka honey has yet to be definitively shown to be effective in the treatment in patients with CRS. An in vivo study by Thamboo et al. [17] evaluated Manuka honey nasal irrigation in patients with allergic fungal rhinosinusitis (fungal infection involving the nasal sinuses) and found a symptomatic improvement during treatment and a small subset of patients demonstrated a significant endoscopic improvement.

Manuka Honey therefore has important clinical implications and could lead to a new approach for treating refractory (non-responsive) CRS. Presently there is only one clinical trial demonstrating safety and efficacy of a Thyme honey nasal spray in CRS [11] and one clinical trial using Manuka honey in CRS showing an absence of adverse effects and improvement in clinical symptoms [17]. Regulatory approved (Australian Therapeutics Goods Administration) antibacterial honey products (Optimel™ Manuka+ Dry Eye Drops and Manuka+ Nasal Spray (Melcare Biomedical Pty Ltd, Australia) are available over the counter for external eye and nasal care. These products are prepared to a rigorous set of standards from a unique proprietary mix of honeys from the Australian and New Zealand Leptospermum species. These honeys are selected for their antibacterial activity, including activity against antibiotic resistant strains such as methicillin resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* [13,18-21]. The aim of this study was to explore the efficacy of Manuka +™ Nasal Spray and Optimel™ Manuka+ Dry Eye Drops in the management of chronic rhinosinusitis and dry eye.

MATERIALS AND METHODS

Participants

Twenty-seven participants between the ages of 50 and 77 years, with a minimum 12 month history of chronic rhinosinusitis and dry eye symptoms, were recruited from the Queensland University of Technology Optometry Clinic. Exclusion criteria included an allergy or sensitivity to bee or honey products, current contact lens wear, current upper respiratory tract infections, nasolacrimal duct conditions, pre-existing corneal conditions, and recent eye surgery. The study complied with the tenets of the Declaration of Helsinki and was approved by the University's Human Research Ethics Committee.

Prior to recruitment, an instillation trial of each Optimel™ honey treatment product was performed to ensure that none of the participants were susceptible to hypersensitivity reactions; none had an allergic response. It was expected that the topical ocular use of honey would produce transient stinging and conjunctival inflammation [22] and that nasal use may produce a temporary but tolerable burning sensation [17]. If protracted inflammation and/or stinging/burning (more than 5 min) were experienced, or any late stage reactions were reported, the participant was excluded from further participation (no participants were excluded for these reasons).

The data collection was performed between July 2015 and June 2016. Five participants did not complete the trial for the following reasons: they were unable to attend the follow-up appointment for unrelated reasons (n=3), they developed a viral upper respiratory tract infection (n=1), or they acquired an unrelated systemic condition (n=1). Only the data of the 22 participants that completed the full 4-week treatment were included in the analysis (Table 1). The mean age of participants were 66±8 years, 14 were females and 8 males.

Table 1. Participant Characteristics at Baseline

Variable	Total	Honey Nasal Spray	Honey Nasal Spray + Honey Eye Drops
Participants (n)	22	10	12
Average Age (year)	66±8	66±8	65±8
Gender (no. male/ female)	8/14	5/7	3/7

Treatments

Participants were randomised to one of two treatment groups: i) Melcare® Manuka +™ Nasal Spray, and ii) Melcare® Manuka +™ Nasal Spray and Optimel Manuka+ Dry Eye Drops (Melcare, Australia). Both products are 16.5% Leptospermum spp. Participants were instructed to use the nasal spray (1-2 sprays per nostril) twice daily (once in the morning and once in the afternoon) and if also provided the eye drops, told to use those twice a day also (one drop per eye in the inferior conjunctival sac).

All dry eye and nasal products were ceased at least two weeks prior to baseline measurements. It was not possible to mask the participants as to the treatment they were using as the participants had to self-administer treatments and the Manuka products have a unique look, smell and taste with nasolacrimal drainage. Before and after each treatment period nasal and dry eye symptomology, ocular surface inflammation, and tear quantity and quality were assessed. The researchers taking the measurements were masked as to the participant's treatment allocation. During the treatment period participants completed a log detailing their usage of treatments and any issues experienced.

Measurements

Participants attended two measurement sessions (baseline, 4 weeks). The study involved both a subjective assessment of nasal symptoms and subjective and objective assessments of dry eye. The validated Sino-Nasal Outcome Test (SNOT-20) was used to assess nasal symptoms [23]. The validated Ocular Surface Disease Index (OSDI) [24], a validated dry eye questionnaire, was used to assess ocular surface

symptoms. Assessment of the tear film and ocular surface were performed objectively using the Keratograph5M (OCULUS Optikgeräte GmbH, Wetzlar, Germany). These assessments included limbal and bulbar conjunctival redness [25] and tear film stability (non-invasive tear break up time (NIKBUT) [26]. The Phenol-Red Thread test (PRT) [27] was used to measure tear secretion. Ocular surface staining was graded using the Oxford Scale [1] and fluorescein tear break up time (FBUT) [28] also measured.

The logbook required participants to record their use of the honey products and record any significant nasal, ocular, or systemic adverse events in their logbooks. Both groups could also use lubricant eye drops if required; 4-5 participants in each group reported using ocular lubricants during the 4 week treatment phase. Compliance with the honey treatments were calculated from the log book as the number of applications actually performed divided by the number of prescribed applications converted to a percent.

Data Analysis

The data of participant's right eyes were selected for data analysis which was conducted using the data analysis program SPSS 17.0 for Windows (SPSS Inc, Chicago, Illinois, USA). Homogeneity of variance was assessed using Levene's Test. Comparison between groups was conducted with parametric independent t-tests for SNOT-20 and OSDI questionnaires, PRT, FBUT, NIKBUT. Non-parametric Mann-Whitney U tests were used to analyse limbal and bulbar redness scores, and Oxford staining scores, as these measures are graded on a scale of 0-4. Treatment effects (baseline vs 4 weeks) within groups were analysed using the either parametric (paired t-test) or non-parametric (Wilcoxon Signed Rank) tests as appropriate.

RESULTS

Adherence

Self-reported adherence to the honey nasal spray when used alone was good to excellent in all participants; reported compliance was excellent in 60%, very good in 20%, and good in 20% (Table 2). Adherence to the nasal spray reduced when both treatments were used concurrently; poor to fair in 42%. Adherence to the honey eye drops was good to excellent in 75% but fair to poor in the others (Table 2). There were no reports of adverse reactions or issues reported in the daily logs.

Baseline Data

Baseline data of the two group was similar except for nasal bulbar redness which was higher in the honey nasal spray group (p=0.014) (Table 3). Both groups had a moderate degree of sino-nasal symptomatology (SNOT-20 > 22.5) [29], and moderate to severe eye symptoms (OSDI =31 for Honey Nasal Spray group (moderate symptoms) and OSDI =38 for the Honey Nasal Spray + Honey Eye Drops treatment group (severe symptoms). Phenol red thread test tear secretion was borderline for tear deficiency (≤10 mm / 15 s is significant) [1]. Fluorescein tear break up and non-invasive tear break up time were reduced, indicating our participant cohort had tear film instability [1], and a mild to moderate degree of ocular surface staining was present [30].

Table 2. Compliance with Treatments.

Self- Reported Compliance Rating	Honey Nasal Spray alone (n=10)		Honey Nasal Spray in combination (n=12)		Honey Eye Drops in combination (n=12)	
	(n)	%	(n)	%	(n)	%
Poor (<50%)	-	-	4	33.3%	1	8.3%
Fair (51-69%)	-	-	1	8.3%	2	16.7%
Good (70-84)	2	20%	-	-	1	8.3%
Very Good (85-94%)	2	20%	-	-	1	8.3%
Excellent (95-100%)	6	60%	7	58.3%	7	58.3%

Table 3. Baseline Data

Measure	Honey Nasal Spray	Honey Nasal Spray + Honey Eye Drops	p
SNOT-20 Score	34±19	34±15	0.98
OSDI Score	31±19	38±26	0.46
Temporal Bulbar Redness	1.4±0.3	1.2±0.4	0.49
Nasal Bulbar Redness	1.7±0.5	1.3±0.5	0.014*
Temporal Limbal Redness	1.0±0.5	0.8±0.3	0.18
Nasal Limbal Redness	1.1±0.5	0.8±0.2	0.07
Phenol-Red Thread Test (mm)	9.8±7.5	11.5±8.0	0.61
NIKBUT (s)	11.7±5.4	11.2±6.7	0.84
FBUT (s)	4.7±2.5	4.6±2.4	0.96
Oxford Stain Score	4.6±3.2	3.1±2.7	0.25

*Baseline data significantly different between groups at p ≤ 0.05.
Data are mean ± SD. Italicized p values represent non-parametric test outcomes.
Abbreviations: SNOT = Sino-Nasal Outcome Test, OSDI = Ocular Surface Disease Index, NKIBUT = non-invasive tear break up time, FBUT = Fluorescein tear break up time.

Table 4. Treatment Effect of Each Group and their Comparison

Measure	Honey Nasal Spray	BL vs Week 4 p	Honey Nasal Spray + Honey Eye Drops	BL vs Week 4 p	Comparison Between Groups p
SNOT-20 Score	-12±15	0.03*	-12±18	0.04*	0.21
OSDI Score	0.2±13.2	0.99	-10.8±15	0.03*	0.09
Temporal Bulbar Redness	0.1±0.3	0.48	0.0±0.4	1	0.46
Nasal Bulbar Redness	0.0±0.5	0.80	0.0±0.4	0.87	0.87
Temporal Limbal Redness	0.0±0.3	0.57	0.1±0.3	0.79	0.67
Nasal Limbal Redness	0.3±0.5	0.96	-0.1±0.2	0.11	0.16
Phenol-Red Thread Test (mm)	-0.3±4.2	0.8	1±7.6	0.66	0.63
NIKBUT (s)	5.5±7.6	0.05	0.5±3.3	0.85	0.18
FBUT (s)	2.6±4.5	0.10	1.3±4.3	0.33	0.49
Oxford Stain Score	-2.3±1.4	0.007*	-1.3±1.6	0.015*	0.09

Data are mean ± SD. *Treatment effect for each group statistically significant at p ≤ 0.05.
Italicized p values represent non-parametric test outcomes.
Abbreviations: SNOT = Sino-Nasal Outcome Test, OSDI = Ocular Surface Disease Index, NKIBUT = non-invasive tear break up time, FBUT = Fluorescein tear break up time.

Treatment Effects at 4 weeks

There were statistically significant improvements from baseline to 4 weeks in both nasal symptoms and Oxford ocular surface staining score for both treatment groups (Table 4) (Figure 1 and 2). In addition the honey nasal spray eye drop combination group also had significant improvement in ocular symptoms (Table 4) (Figure 3). There were no statistically significant improvements in the other measures and no significant differences between the two treatments (See Table 4).

No important adverse events were recorded in the logbooks. As expected, symptoms reported included nasal discharge, dry eye and red eyes. Comments indicating improvement included "relieves nasal congestion" and "eyes feel lubricated".

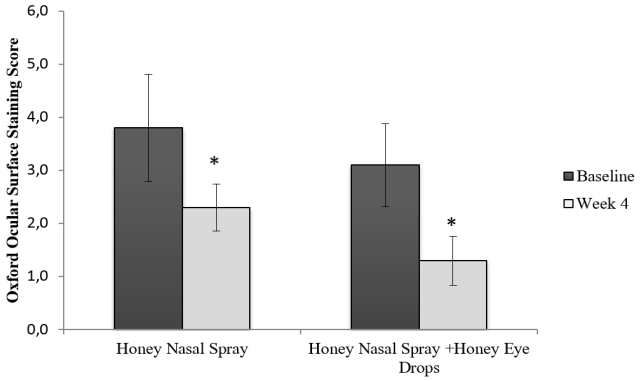

Figure 2. Oxford Ocular Surface Stain Scores at baseline and following 4-weeks of treatment in the Honey Nasal Spray and Honey Nasal Spray + Honey Eye Drops treatment groups. Data are mean ± SD. * Indicate differences between baseline and week 4 significantly different at p<0.05.

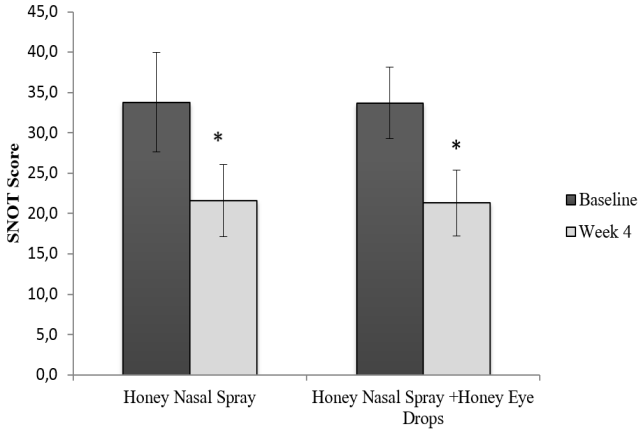

Figure 1. Sino-Nasal Outcome Test (SNOT-20) scores at baseline and following 4 weeks of treatment in the Honey Nasal Spray and Honey Nasal Spray + Honey Eye Drops treatment groups. Data are mean ± SD. * Indicate differences between baseline and week 4 significantly different at p<0.05.

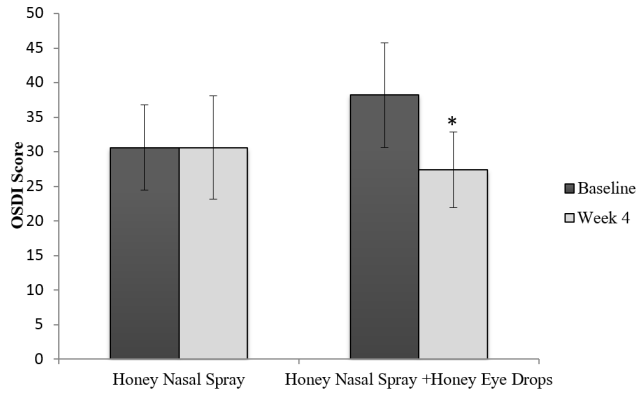

Figure 3. Ocular Surface Disease Index (OSDI) scores at baseline and following 4-weeks of treatment in the Honey Nasal Spray and Honey Nasal Spray + Honey Eye Drops treatment groups. Data are mean ± SD. * Indicate differences between baseline and week 4 significantly different at p<0.05.

DISCUSSION

Our finding of improvement in nasal symptoms (with the SNOT-20 questionnaire) in rhinosinusitis suffers using a honey nasal spray for 4 weeks, supports the findings of Thamboo et.al [17] who also reported improved symptoms in allergic fungal rhinosinusitis sufferers using a 50% Manuka honey over a similar time frame. Their study involved using one nostril as a control, i.e. the nasal spray was only applied to one nostril. *Leptospermum spp.* honey, has been demonstrated to be safe, non-toxic and to have both antimicrobial and anti-inflammatory effects on the ocular surface mucosa when applied undiluted topically in dry eye disease [22, 31], and diluted (16.5% to 50%) to the sino-nasal mucosa in rhinosinusitis [17, 32].

The mechanisms by which nasal symptomatic improvements were achieved with the honey nasal spray remains to be investigated. Bacterial biofilms are thought to play a significant role in the pathogenesis of chronic rhinosinusitis [33]. Manuka (*Leptospermum scoparium*) honey has shown strong anti-biofilm activity against *S. aureus*. [14] This effect has been shown to be primarily due to uniquely high levels of the phenol compound, methylglyoxal (MGO), within Manuka Honey [34-35]. Jervis-Bardy et al. [15] demonstrated a synergistic anti-biofilm effect when augmenting Manuka Honey with additional MGO, requiring 16.5% wt/vol Manuka Honey with 0.53 mg/mL MGO to achieve complete *S. aureus* biofilm eradication. Further studies have shown that the MGO concentration required for anti–*S. aureus* biofilm activity ranged between 0.5 and 3.6 mg/mL [36].

Thamboo et al. [17] qualitatively assessed ethmoid cavity swabs pre and post one month of nasal *Leptospermum spp.* honey spray treatment but did not find any consistent treatment effect of honey. We did not perform nasal swabs for colony forming units in this study but have previously demonstrated topical application of pure *Leptospermum spp.* honey applied to the conjunctival sac thrice daily significantly reduced conjunctival and lid margin (predominantly Staphylococcal spp.) colony counts in individuals with dry eye disease [31]. Further studies are required to determine if topical ocular and/or nasal inhalation of medical grade *Leptospermum spp.* honeys impact the nasal mucosal flora and the optimal concentrations at which these effects are achieved.

We found a statically and clinically significant improvement [37] in dry eye symptoms (OSDI after 4 weeks) in the group using the combined honey nasal spray eye drop treatment but not the nasal spray alone. Honey eye drops used over similar timeframe have been demonstrated to improve dry eye symptoms and signs [31, 38]. This may mean that the eye drop product needs to be added to control dry eye symptoms and that the nasal spray alone is not helpful in dry eye. Alternately it may indicate that a longer time frame is needed to observe an improvement in eye symptoms from using just a honey nasal spray. Given the connection between the eye and the nose [5], effects of indirect treatments would be expected, but it would not be surprising if these were slower to observe. It would also be useful to determine if honey eye drops alone have effects on nasal symptoms in sufferers of both dry eye and rhinosinusitis.

Dry eye patients have high prevalence of symptoms of ocular allergy due an insufficient tear and/or unstable tear film prolonging contact of allergens and irritants incident on the ocular surface [39]. Our participant group was characterised by both a borderline tear deficiency and poor tear film stability. Previous studies have demonstrated that intranasal steroidal sprays can improve symptoms of season and perennial ocular allergy (tearing, redness and itch) [40]. One proposed mechanisms for this effect is that inhaled allergens and irritants may induce ocular symptoms by means of the naso-ocular reflex and it is thought that these intranasal steroids hinder the development of allergic ocular symptoms by inhibiting the initiation of the naso-ocular reflex [40]. Another proposed mechanism is that intranasal steroids also decrease nasal inflammation and oedema in the inferior portion of the nasolacrimal duct, and may allow for improved drainage of ocular secretions and decreased ocular exposure to allergens and inflammatory mediators [40]. Whilst ocular symptomatic improvements were not achieved with use of lone honey nasal spray treatment, there were statistically and clinically significant improvements [30] in corneal staining in both treatment groups; suggesting that there were ocular benefits of the lone honey nasal spray treatment. The improvement in the integrity of the corneal epithelium adds to the growing body of evidence that some honeys, including *Leptospermum* spp. honeys can improve corneal epithelial integrity [22] and promote corneal epithelialisation [41, 42].

In this study, poorer adherence to dual honey eye drop and nasal spray treatment was reported by our participants. Adherence to home-based dry eye therapies is traditionally poor, particularly where the regime is prolonged or time consuming [4, 43]. Whilst twice daily instillation of two topical treatments arguably does not require significant effort, our middle aged to elderly participants may well have been managing multiple other chronic medical issues with home-based treatments in addition to participation in this study. On average, patients with chronic medical conditions take from 30% to 70% of the prescribed medication doses and on average 50% discontinue medications in the first months of therapy [44]. The glaucoma ophthalmic literature shows similarly low rates of adherence to treatment [45]. Similar to topical glaucoma eye therapy, instillation of both the honey drops and the nasal spray typically induces temporary local irritation which is likely to most adversely affect the compliance of dual therapy. Nevertheless, medically regulated *Leptospermum spp.* antibacterial honey products have numerous practical advantages in the chronic care of dry eye and rhinosinusitis: low cost, over-the-counter, sterile, non-benzalkonium chloride preserved, non-cytotoxic with frequent dosing and long term dosing, multi-dose, broad spectrum, unaffected

by room temperature and UV and extended shelf life [22, 46-49].

Limitations of this study were the relatively small study population (n=22) and short treatment duration (4 weeks), and lack of inclusion of a lone honey ocular treatment arm. Longer treatment durations of 3 months in a larger group of participants would be required to assess changes in ocular and nasal clinical signs with honey treatments in individuals with concurrent dry eye and rhinosinusitis. As it is not possible to mask the treatment from the participants it is possible that some of the subjective improvement in symptoms was due to a placebo effect.

CONCLUSIONS

Manuka honey nasal sprays appear to be a promising safe and low cost remedy for improving symptoms of chronic rhinosinusitis.

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