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Original article

The effect of standardized honey on mucosal healing of the nose and paranasal sinuses after polypectomy: A randomized controlled, double blind pilot study

Rahman Movahed[1], Omid Rajabi[2], Hoda Azizi[3], Sogol Jafari[4], Razieh Yousefi[5], Mehdi Bakhshaee[1]

[1] Sinus and Surgical Endoscopic Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; [2] Department of Drug and Food Control, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran; [3] Department of Complementary and Chinese Medicine, School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; [4] Department of Pharmacology, International Pardis Pharmacology University of Tehran, Tehran, Iran; [5] Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran.

Abstract. *Objectives:* Nasal polyposis (NP) is a chronic inflammatory disease. Honey has several anti-microbial, anti-oxidants, healing, and anti-inflammatory properties which may reduce the need for steroids in this situation. Therefore, the aim of this study is to show the effect of standardized honey on mucosal healing of the nose and paranasal sinuses after polypectomy. *Design and method:* In this double-blind, randomized, placebo-controlled clinical trial, 28 patients with nasal polyposis underwent functional endoscopic sinus surgery (FESS). Besides common post-op medications, normal saline (as placebo) and diluted processed honey were used separately in the two nostrils of each patient. Two endoscopic follow-ups using the Philppot-Javer (P-J) scoring system were performed to assess the healing and recurrence of polyps on either side. The secondary outcome measure was the patients' satisfaction rate. *Results:* The patients' mean age was 38.03±11.9 years. 15(57.7%) had a positive prick test and also 15(57.7%) had dense eosinophilic infiltration in their surgical specimens. In the first and second follow-up sessions, total P-J scores showed better results for honey in comparison to the normal saline side but that results were not significantly different (P=0.93, P=0.07); whereas it is fair to say that in the second follow-up, the ethmoid and maxillary sinuses demonstrated a greater difference compared to the other sites based on their averages but there were not significantly meaningful (P=0.05, P=0.06). The total score also showed better results for honey in comparison to the normal saline side, but statistically insignificant (P=0.07). *Conclusion:* Diluted honey seems to have certain positive effects in reducing post-operative edema and the recurrence of nasal polyps in at least the ethmoid and maxillary sinuses; although this positive effect did not result in significant changes. (www.actabiomedica.it)

Key words: Honey, Nasal polyposis, Paranasal sinuses, endoscopic sinus surgery, Mucosal healing

1. Introduction

Nasal polyposis (NP) is a chronic inflammatory disease affecting the nasal mucosa and paranasal sinuses, leading to the formation of polyps. Its prevalence ranges from 0.2-5.6% in the literature (1-3), depending on the diagnostic criteria used in each study. Cadaveric studies have reported it to be as high as 32% in the normal population (4). Corticosteroids are the mainstay of the treatment but for patients unresponsive to medical therapy, fine endoscopic sinus surgery (FESS) is an invaluable adjunct to the treatment plan.

The use of honey for medicinal purposes reaches back to 4000 years before when Sumerian tablets were

used in various recipes and dressings (5). Honey is an acidic product (PH=4) with a chemical composition that varies depending on the flowers from which it is derived. Its components are 80% sugar, 17% to 20% water, and 4% various other substances (pollen grains, proteins, enzymes, hydrogen peroxide, amino acids, organic acids, polyphenols, vitamins minerals). Due to honey's low water concentration, the growth of micro-organisms (yeasts, fungi, bacteria) is prevented (5).

It should be noted that honey is not a sterile compound and may contain two important bacterial species, *B. subtilis* and *C. botulinum (6)*. Interestingly, it can be sterilized by gamma radiation (2.5cGy) without losing any of its biological properties (7).

Antiseptic and healing properties are the two main biological effects of honey which are attributed to two factors: hydrogen peroxide (H2O2) and hyper osmolality (8, 9).

The benefits of honey in the head and neck area mentioned in the literature include the treatment of salivary fistulas following major head and neck surgeries (10), recurrent labial herpes disease (11) and wound healing enhancement (12). However, at the time we initiated our study, the data regarding the use of honey in the sinonasal apparatus was limited to a single well-organized study by Thamboo et al. (13).

Herein and for the first time in Iran, we processed a specialized honey preparation consisting of one of the best natural honey originated from the eastern gardens of Birjand. We aimed at assessing its effect on mucosal healing and probably the recurrence of sinonasal polyposis after endoscopic sinus surgery. Due to a lack of sufficient data regarding honey application in the nose especially following surgery which has a certain risk of harmful reactions and serious infections, this study was designed as a pilot survey to determine the actual effect of this natural medication on patients' satisfaction and the disease outcome.

2. Materials and Methods

2.1. Study design and participants

In this double blind, randomized, placebo-controlled clinical trial, patients with a history of nasal stiffness, rhinorrhea, post nasal dripping, smell disorders and other similar symptoms suggestive of chronic rhinosinusitis were evaluated and underwent a thorough physical examination in Imam Reza educational Hospital, Mashhad, Iran from March 2015 to September 2017.

Patients with unilateral involvement of the nasal cavity, coagulopathies and hemorrhagic disorders, genetic predisposing factors (i.e. Cystic Fibrosis), any form of immunodeficiency or immunosuppression, suspicious or proved neoplastic pathology, age under 13 years and history of any kind of allergy or hypersensitivity to bees, honey and honey byproducts were excluded from the study. Skin prick testing was also performed for each case prior to enrollment for common local aeroallergens and honey by a single immunologist.

Among those with a confirmed diagnosis of nasal polyposis based on physical examination and imaging modalities, 36 patients were enrolled in the study. The sinonasal outcome test 22 (SNOT-22) questionnaire was filled out by every participant once at study entrance and once again at the end of the study course in order to evaluate the overall treatment efficacy and patient satisfaction rate.

Rhinosinusitis with polyposis grading was accomplished both by endoscopic study (Lund-Kennedy score) and by imaging through computed tomography (Lund-Mackay score).

2.2. Sampling

Informed consent was signed by each patient regarding the drug application, its possible complications, and outcomes. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences.

Functional endoscopic sinus surgery (FESS) was performed for all patients and the same protocol was recruited for the post-operative medical treatment of every case. It included oral prednisone 15 mg per day for 5 consecutive days, anti-histamine therapy in allergic patients (oral cetirizine 10 mg once daily), corticosteroid nasal spray (Fluticasone propionate 1 puff in each nostril twice a day) and antibiotics (amoxicillin 500mg three times a day) for 7 days.

2.3. Randomization and blinding

In addition to the standard medical therapy, nasal irrigation with the formulated honey solution spray was administered to one nostril and normal saline (NaCl 0.9%) was sprayed into the other nostril of each patient as a control (both four times a day). Both the patient and the physician were completely blind to the nostril in which the honey was administered and randomization was done by the pharmacist who provided the drugs to the patients. The bottles were made as much identical as possible in order to minimize biases.

2.4. Interventions

All subjects were instructed to commence saline and honey irrigation on the 2nd post-op day. The primary follows up session was in the 4th post-op week in which anterior rhinoscopy with adequate debridement was done in the office base setting. On the second post-op visit in the 12th week, atraumatic local nasal endoscopy was performed in the operating room. Using the Philppot-Javer (P-J) scoring system (13), quantification was performed based on edema, polyp formation and mucus presence. During these follow up sessions photographs were taken from the endoscopic view of each nasal cavity and the pictures were reviewed by another rhinologist. Any complications such as burning sensation and synechia was recorded as an open set questionnaire.

2.5. Honey preparation and quality

The honey used in our study was provided from the beehive of Birjand gardens, a city in eastern Iran, in which the bees had fed from Jujube (Zizyphus jujuba Mill) and barberry wild trees (berberis). Honey was initially dissolved in the buffered solution with a ratio of 20% w/w and it was passed through the WATTMANN 42 paper filter by a Büchner funnel under vacuuming conditions. This solution was then autoclaved at 121 °C (249°F) for 18 minutes.

Under sterile conditions, a sample of the solution was transferred to the Swine Casein Broth medium and kept at both 25°C and 37°C for 24 hours. A negative result was obtained for both temperatures which meant sterility of the honey solution. This natural honey underwent physical, chemical, and microbiological analysis before dilution. The viscosity, ingredients composition, anti-oxidative activity, MIC (mean inhibitory concentration), and other physicochemical specifications were analyzed by an experienced pharmacist and are outlined in the Results section.

After providing honey from natural beehives, it underwent complete biochemical analysis according to standard protocols as shown in Table 1 and 2.

Table 2 shows that despite the chemical processing and autoclaving of honey, its antibacterial properties have been well preserved.

2.6. Statistical analysis

Statistical analyses were performed using statistical software (SPSS version 16; SPSS Inc., Chicago, IL). Inferential analysis was mainly performed through paired and independent T-test. Data were expressed as mean±standard deviation (SD) for continuous variables. The significance level was maintained at 0.05 in all tests.

Table 1. Chemical properties of the honey (Flame absorption spectrometry. Analytical methods. (1989). Varian Australia Ply Ltd., Mulgrave, Vic., Australia).

Sample	Nitrogen (mg/100g)	pH	acidity total (meq/Kg)	Ash content	Moisture content	Viscosity (in 25c)
Honey	57.9±0.66	4.3±0.4	53.3±2.33	0.2289±0.008	19.88±9.22	85 Cp

Table 2. Minimum inhibitory concentration (MIC) and minimum antibiotic concentration (MAC) of the processed honey against *S. aureus and P. aeruginosa.*

Species	Staphylococcus aureus		Pseudomonas aeruginosa	
	MIC	MAC	MIC	MAC
	0.5	-	0.5	0.5

Results

In this study 36 patients were enrolled, of whom 8 (22%) failed to use the honey product and placebo appropriately and were excluded from the study analysis (Fig. 1).

The mean age of the 28 remaining patients was 38.03±11.9 years (range:13-63 yrs); 15 (53.6%) patients were male and 13 (46.4%) female.

Nasal obstruction was the most common chief complaint with 23 (82.1%) cases followed by anosmia and headache. Asthma was the most common

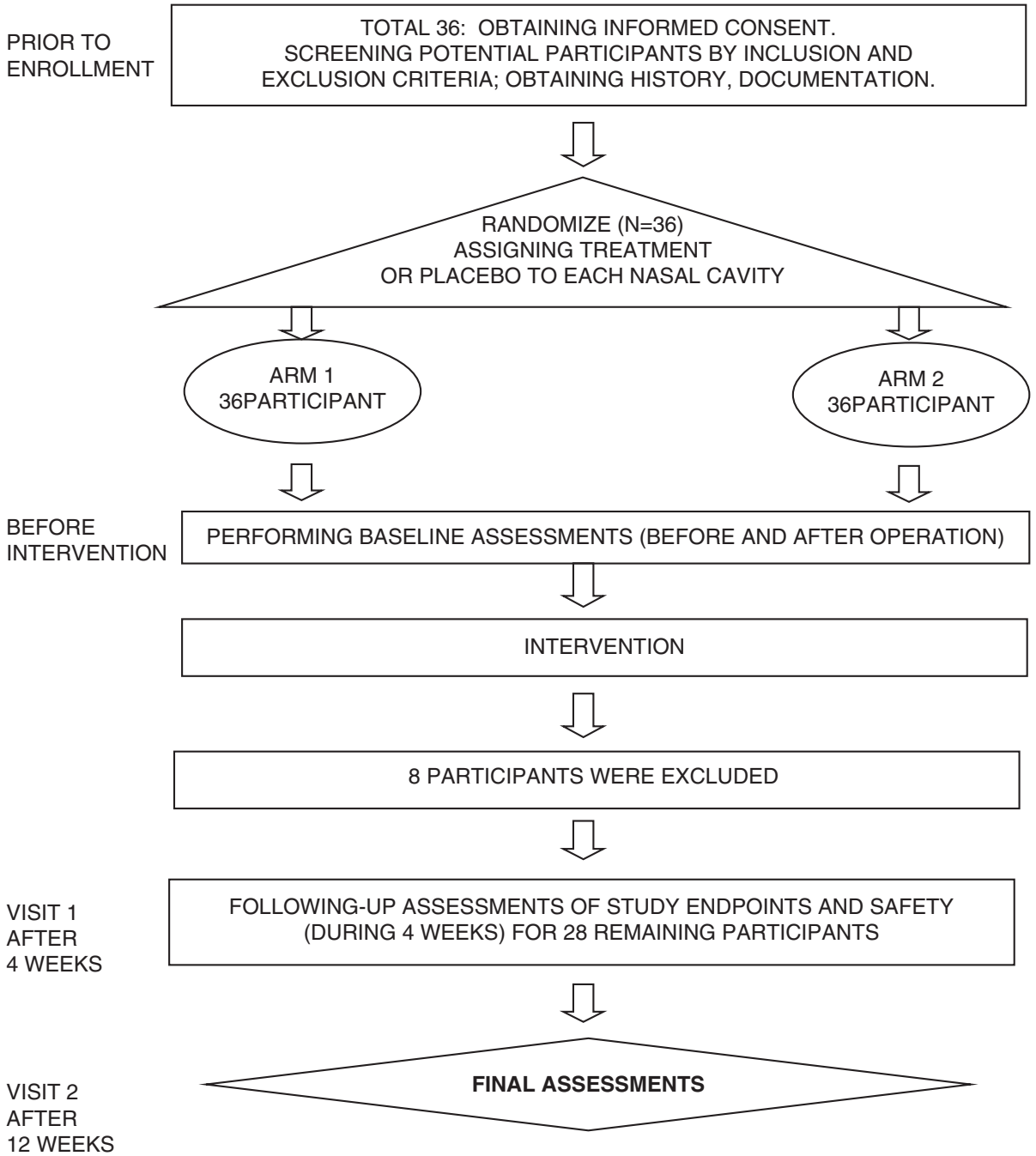

Figure 1. Enrolment of patients into study

accompanying morbidity among our studied individuals involving 15 (53.6%) cases. Regarding irritant exposure as a risk factor for this condition, passive smoking was the most common irritant with 3 (10.7%) cases prevalence, yet second to "No risk factor" in 23 (82.1%) patients.

Pre-operative Lund-Mackay scoring system revealed a mean score of 19.53±4.15 on both sides (ranging from 10 to 24 with a median of 20.00) which is above the average. The pre-operative mean Lund-Kennedy score was 9.96±1.20 (ranging from 8 to 12 with a median of 10.00).

SNOT22 was used to subjectively self-assess the patients' rhinosinusitis symptoms pre and post-operatively in both nostrils. Using a paired sample T-test a statistically significant improvement in patients' symptoms following treatment was observed (P=0.000).

In total, 26 patients underwent skin prick testing with common native aeroallergens and also the diluted honey, out of which 15 (57.7%) had a positive prick test and 11 (42.3%) had negative results. Independent T-tests did not show any correlation between Lund-Kennedy, Lund-Mackay, and SNOT22 (pre-op) mean scores and skin prick test results, and significant test results were P=0.85, P=0.36, P=0.61 respectively. Moreover, 15(57.7%) patients had dense eosinophilic infiltration in their surgical specimens on histological examination while the other 11 (42.3%) cases showed mild scattered eosinophils throughout the tissue sample. Also, asthma is significantly related to the presence of this dense eosinophilic infiltrate in the patients' nasal mucosa (P=0.01). Again, disease severity in terms of objective (LK and LM) and subjective (SNOT-22) evaluation showed insignificant correlation with this histological finding (P=0.38, 0.57, and 0.11 for Lk, LM, and SNOT-22 respectively).

Herein, we also compared the 5-point reduction and mean reduction rate of the P-J scores in the honey arm between patients with dominant eosinophilic mucosa and the other cases. No correlation was found between the presence of dense eosinophilic infiltration and the reduction of the score (P=0.68 for the 5-point reduction and P=0.71 for mean reduction). Similar results were obtained for the correlation of the skin prick test and improvement in the honey arm (P=1.00 for the 5-point reduction and P=0.52 for mean reduction).

One patient had a positive prick test result for the honey preparation and showed a mild reaction to the antigen. This particular patient got higher scores in post-operative endoscopic examinations but as the patient's prick test results had been lost, honey was administered for 12 whole weeks. The honey-side nostril in this patient showed a deteriorating status during this time but with no significant adverse events.

In the following, a paired sample t-test was used to examine the improvement or deterioration in each study arm. In the first follow-up session, no significant difference was found between the two arms regarding polyps' regrowth using the P-J scoring system in any distinct sinus. Similarly, the final total score was not significantly different between the honey and placebo sides either (P=0.93). In the second follow-up session, again no significant difference was found between the two groups in the P-J scores, although in the ethmoid (P= 0.05) and maxillary sinuses (P= 0.06) this difference was more remarkable than other sites; yet in the sphenoid sinus in both the first and second endoscopic follow-ups this change was minimum. The total score also showed better results for honey in comparison to the normal saline side, but statistically insignificant (P=0.07) (Table 3).

Table 3. Comparison of the P-J scores between the honey and placebo arms for the first and second visits.

	First visit		Second visit	
Anatomic site	**Mean±SD**	**sig**	**Mean±SD**	**sig**
Frontal(Honey) Frontal(Placebo)	3.39± 2.39 3.68±2.78	0.3	3.12± 1.75 3.28±1.72	0.61
Maxillary(Honey) Maxillary(Placebo)	3.43±2.22 3.28±1.92	0.74	2.5± 1.62 3.36±2.41	0.06
Ethmoid(Honey) Ethmoid(Placebo)	3.75±2.25 3.82±2.16	0.83	3.07± 1.86 4±2.16	0.05

Table 3. (*Continued*)

Anatomic site	First visit		Second visit	
	Mean±SD	sig	Mean±SD	sig
Sphenoid(Honey) Sphenoid(Placebo)	3.32±2.54 3.32±2.64	1	3.11 ±1.98 3.14±1.92	0.91
Mucin(Honey) Mucin(Placebo)	2.53±1.57 2.75±1.48	0.4	1.78 ±1.71 2±1.7	0.5
Total score(Honey) Total score(Placebo)	13.89±7.54 14±8.43	0.93	11.75 ±6.06 13.82±6.01	0.07

As presented in Table 4, in the honey arm, the changes in the Maxillary sinuses and Mucin production have improved over time (P=0.005, P=0.03 respectively) and the total score was also statistically significant (P= 0.03). On the other hand, in the placebo arm, the changes only in Mucin amount have improved over time.

Finally, No significant or morbid adverse effects were observed during the follow-up periods, even in the single honey-sensitive patient. The McNemar test revealed no statistically meaningful difference between the two groups regarding any complication. Burning and itching were recorded with a much higher prevalence in the honey group, yet this difference did not reach statistical significance (P=0.06).

Discussion

Treatment of nasal polyposis consists of multiple medical and surgical modalities each of which has certain benefits and disadvantages. Medical therapy is the mainstay of treatment but in reluctant cases, surgical management seems inevitable to relieve the patients' symptoms.

Corticosteroids are the most effective treatments and if administered topically, the first-line choice of medication for the treatment of sinonasal polyposis both pre- and post-operatively. Several attempts have been made to find other supplementary treatments that could reduce the need for steroids or even substitute them, but no data was found on the association between honey and mucosal healing of the nose and sinuses. So the present study was designed to determine the effect of standardized honey on mucosal healing of the nose and paranasal sinuses after polypectomy.

At first, the current study found that nasal obstruction was the most common chief complaint followed by anosmia and headache, and Asthma was the most common accompanying morbidity among our studied individuals.

Table 4. Philppot-Javer score difference from 1st to 2nd follow-up visit in each sinus cavity (n=28)

Anatomic site	Honey		Placebo	
	Mean±SD	sig	Mean±SD	sig
Frontal first visit Frontal second visit	3.39± 2.39 3.12±1.75	0.5	3.68± 2.78 3.28±1.72	0.43
Maxillary first visit Maxillary second visit	3.43±2.22 2.5± 1.62	0.005	3.28± 1.92 3.36±2.41	0.9
Ethmoid first visit Ethmoid second visit	3.75±2.25 3.07± 1.86	0.1	3.82± 2.16 4±2.16	0.7
Sphenoid first visit Sphenoid second visit	3.32±2.54 3.11 ±1.98	0.6	3.32 ±2.64 3.14±1.92	0.76
Mucin first visit Mucin second visit	2.53±1.57 1.78 ±1.71	0.03	2.75 ±1.48 2±1.7	0.03
Total score first visit Total score second visit	13.89±7.54 11.75±6.06	0.03	14 ±8.43 13.82±6.01	0.9

The mean scores of Lund-Mackay, Lund-Kennedy and, SNOT-22 tests were relatively high and above the average which demonstrates the higher grades of involvement in the patients enrolled in this study. This is important because higher degrees of nasal polyposis, especially when associated with asthma, can be the main cause of recurrent disease and treatment failure (14).

Among CRS patients undergoing sinus surgery, the prevalence of positive skin prick testing ranges from 50 to 84 percent, of which the majority of patients (60%) have multiple sensitivities (15, 16). In contrast, Drake-Lee (17) reported that positive skin test results are not more common than what is expected in patients with nasal polyps (25%), causing the presence of allergy to seem as a coincident. The rate of positive skin prick tests was 57.7% in our study. The positivity or negativity of the prick test seemed unrelated to disease severity as we matched pre-operative SNOT-22, LM, and LK scores with the prick test results with a p-value of 0.61, 0.85 and 0.36, respectively. Therefore, although allergy is a risk factor in the pathogenesis of chronic rhinosinusitis with polyposis, the severity of the disease does not seem to be related to its presence. This has also been previously reported by other authors (18). The present study suggests that CRS is an inflammatory disease that occurs independently from systemic IgE-mediated pathways.

In the histopathology of nasal polyposis, a typical finding is the presence of intense inflammatory cell infiltration within the stroma, with eosinophils' predominance. In the subset of Widal or Samter triad (including asthma, NSAID intolerance, and nasal polyposis) eosinophilic infiltration is more dominant (19). In our study a greater number of patients had dense eosinophilic infiltration in their surgical specimens on histological examination throughout the tissue sample. As previously mentioned asthma and bronchial hyper-responsiveness are the conditions in which this histopathological pattern is mainly observed, as well as AFRS (allergic fungal rhinosinusitis). In the current study we did not examine the patients and their specimens for evidence of AFRS; however, asthma is significantly related to the presence of this dense eosinophilic infiltrate in the patients' nasal mucosa. Again, disease severity in terms of objective (LK and LM) and subjective (SNOT-22) evaluation showed a nonsignificant correlation with this histological finding.

In the current study on the first follow-up session, we found no significant difference between the two groups neither for any individual sinus nor for the total score. This was the same for a similar study at this same follow-up point (14). In the second follow-up session, again no significant difference was found between the two groups in the P-J scores, although in the ethmoid and maxillary sinus this difference was more remarkable than other sites. The findings observed in this study mirror those of the previous studies that used the 5-point reduction scoring system to evaluate the improvement rate, in that study, 10 cases (35.71%) in the honey arm had at least five scores reduction, yet 9 cases (32.14%) in the placebo arm showed such a difference which again shows no superiority for honey either (P=0.41) (13).

Comparison of the 5-point reduction and mean reduction rate of the P-J scores in the honey arm between patients with dominant eosinophilic mucosa and the other cases Confirms that the presence of dense eosinophilic infiltration is not associated with the reduction of the scores. Similar results were obtained for the correlation of the skin prick test and improvement in the honey arm. So the present findings seem to be consistent with Thamboo et al. study who found better results in patients with high IgE levels in the honey group, no such relationship was achieved in our study; although the two methods used for identifying atopy were not fully identical (13).

To our knowledge, Thamboo et al. were the first who used honey in nasal polyposis, in vivo and inhuman species. In that study, patients were assessed after 30 days and no meaningful correlation was found between honey application and better scores. Therefore, we extended the follow-up period (12 weeks) to measure the longer-term outcomes. As there are no studies regarding the ideal dosing of honey in this regard, and as in Thamboo's study the spray was used twice daily, we decided to augment the dose in our study.

Nevertheless, we should not overlook the process the honey underwent in this study; PH neutralization and losing the osmotic characteristics of the honey may have led to its lower anti-bacterial effects and therefore

lower biofilm eradication which has an important role in CRS pathogenesis (19). No study so far has evaluated the effect of thermal injury on the protein and enzymatic content of honey. So the actual effect of honey in the respiratory mucosa may differ from that of in diabetic foot, bedsores or mucositis because of the processes it needs to be undergone to become feasible in the nasal cavity, especially when an infection is a concern in the highly vascular ulcerated bed.

Although the achieved results are consistent with previous studies, in contrast, we found better results for the ethmoid and maybe the maxillary sinus. One of the acceptable explanations could be the physicochemical characteristics of our solution. Maybe the drug delivery to the farther sinuses was not enough because of high viscosity of the preparation or the inefficient flow for the honey in the nasal cavity, it is somehow apparent that the nearest the sinus cavity was, the better the results were; with the worst results for the sphenoid and frontal sinuses. Moreover, considering the healing course of the mucosa during the study, one can assume that with a longer treatment course, better results could be achieved.

Taken together, we encountered a major conflict during the study, that higher viscosity leads to better adhesion and thus better effectiveness, but a special pump is needed to vaporize and make the appropriate droplet size and velocity. Lower viscosities may provide better distribution in the nasal cavity but are prone to accelerated clearance. Further investigations are required to better determine the optimal characteristics of the honey to be used as a nasal spray.

Limitations and obstacles

Being the first study in Iran to use honey products in nasal cavities, we expected a reasonable number of dropouts due to unexpected side effects, patients' intolerance, problems with drug provision by patients, and inappropriate drug use based on cultural and social factors. So one source of weakness in this study that could have affected measuring honey effect was the small sample size, and further research investigating this effect would be very interesting.

Purchasing the natural honey on the appropriate season, the spray bottle ordering and shipping, biochemical analysis, titration and dilution processes, and most importantly persuading patients to continue their follow up sessions in an in-patient setting were the most problematic and time-consuming obstacles the authors had to overcome.

Conclusions

In this study, honey failed to show superior effects on sinonasal polyposis recurrence and healing properties in comparison to normal saline. Nevertheless, no noteworthy adverse effect was detected except for a mild burning sensation. Processing the honey may have unknown effects on its healing and antimicrobial properties which ought to be explored. Different response patterns in each sinus may represent the inefficient flow of the solution. Therefore, future studies with new formulation or better route of delivery and of courses with longer treatment course may give promising results.

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Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Correspondence:
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Mehdi Bakhshaee, MD.
Associate Professor of Otorhinolaryngology-Head & Neck Surgery, Sinus and Surgical Endoscopic Research Center, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
Tell/Fax: +985138022517
E-mail: Mehbakhsh@yahoo.com; Bakhshaeem@mums.ac.ir