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Single-Blind Study of Manuka Honey in Allergic Fungal Rhinosinusitis

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ABSTRACT

Background: **Some patients continue to suffer from symptoms of sinusitis after maximal topical medical and surgical treatment for allergic fungal rhinosinusitis (AFRS). Manuka honey has well-documented antimicrobial and antifungal properties and is currently being used by physicians across the world for a wide variety of medical problems.**

Objective: **This study aimed to determine the effectiveness of Medihoney Antibacterial Medical Honey in patients who continue to suffer from AFRS resistant to conventional medical treatment after bilateral functional endoscopic sinus surgery and maximal postoperative medical management.**

Methods: **A randomized, single-blind, prospective study was conducted at a tertiary centre. Thirty-four patients with AFRS sprayed one nostril with 2 mL of a 50/50 mixture of honey-saline solution once a day at night for 30 days. Otherwise, patients continued with their regular nasal regimen in both nostrils. A 5-point improvement in our clinic's endoscopic grading system was considered significant. During their pre- and postassessment, patients' sinus cavities were cultured, and the patients filled out a Sino-Nasal Outcome Test (SNOT-22) questionnaire to assess subjective nasal symptoms.**

Results: **As a group, the 34 patients who completed the study showed no significant improvement in the treated nostrils versus control nostrils ($p = 1.000$). However, the nine patients who did respond to the honey treatment relative to their control side responded very well. A number of these patients had high IgE levels in their blood. The manuka honey did not appear to modify the culture results in the ethmoid cavities after 30 days of treatment, but patients who completed the SNOT-22 questionnaire indicated global improvement in their symptoms while receiving the honey spray ($p = .0220$).**

Conclusion: **Overall, topical manuka honey application in AFRS, despite showing symptomatic benefits, did not demonstrate a global improvement in endoscopically staged disease, but specific patients did show significant positive responses. Further research is needed to determine the factors of the patients who responded well to the honey spray, which may correlate to high IgE levels.**

SOMMAIRE

Contexte: **Certains patients continuent à souffrir de symptômes de rhinosinusite fongique allergique (RFA) après un traitement médical topique maximal et un traitement chirurgical. Le miel de manuka a des propriétés antimicrobiennes et antifongiques bien documentées, et les médecins l'utilisent actuellement, un peu partout dans le monde, afin de traiter une multitude de problèmes médicaux.**

Objectif: **L'étude avait pour objectif de déterminer l'efficacité du miel médical antibactérien Medihoney chez des patients qui continuent à souffrir d'une RFA résistante au traitement médical classique après une chirurgie endoscopique bilatérale des sinus et un traitement médical postopératoire maximal.**

Méthodes: **Un essai prospectif, à répartition aléatoire et à simple insu a été mené dans un centre de soins tertiaires. Nous avons demandé à 34 patients souffrant d'une RFA de vaporiser, dans une narine, 2 mL d'un mélange de miel et de solution physiologique salée, préparé dans des proportions égales, Un fois par jour, le soir, pendant 30 jours; aucun autre changement n'a été apporté au traitement nasal habituel dans les deux narines. Une amélioration de 5 points, selon le système d'évaluation endoscopique utilisé à la clinique, est jugée importante. Au cours des évaluations pré- et postopératoires, il y a eu culture des cavités sinusales, et les patients ont rempli le questionnaire Sino-Nasal Outcome Test (SNOT-22) sur les symptômes nasaux subjectifs.**

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Résultats: **Dans l'ensemble, aucune amélioration importante des narines traitées par rapport aux narines témoins n'a été observée chez les 34 patients qui ont terminé l'étude ($p = 1.000$). Par contre, neuf patients ont réagi au traitement à base de miel, et la réaction était considérée comme très forte par rapport aux narines témoins. Certains de ces patients avaient un taux élevé d'IgE dans le sang. Le miel de manuka n'a pas semblé modifier les résultats des cultures des cavités pneumatiques de l'ethmoïde, après 30 jours de traitement, mais les patients qui ont rempli le questionnaire SNOT-22 ont fait état d'une atténuation générale des symptômes pendant le traitement par vaporisation de la solution de miel ($p = .0220$).**

Conclusion: **Dans l'ensemble, l'application topique de miel de manuka dans le contexte de la RFA ne s'est pas soldée par une diminution générale de la maladie, évaluée à l'endoscopie, et ce, malgré un soulagement des symptômes, mais une réaction sensiblement favorable a été observée chez certains patients. Il faudrait poursuivre la recherche afin de déterminer les facteurs de réaction favorable à la vaporisation d'une solution de miel, qui pourrait être en corrélation avec un taux élevé d'IgE.**

Key words: *allergic fungal rhinosinusitis, manuka honey, sinusitis*

Allergic fungal rhinosinusitis (AFRS) is a chronic disease, and the nature of its etiology and pathogenesis has been subjected to much debate, even among current experts in the field of rhinology. The characteristic features of the disease were described by Bent and Kuhn (Table 1).[1] Although the lack of current understanding of this heterogeneous group of patients does not allow for curative treatment, AFRS can be successfully managed by meticulous surgery and careful regular postoperative follow-up. However, some patients prove refractory to medical treatment postoperatively. At our centre, standard medical treatment includes twice-daily budesonide irrigations (Pulmicort 0.5 mg/2 mL nebules added to 240 mL of saline via a NeilMed sinus rinse bottle [NeilMed Pharmaceuticals, Santa Rosa, CA]). Anecdotal evidence has come to light to suggest that manuka honey may be a useful new weapon to combat AFRS.

Honey has never been documented as a form of medicinal treatment in sinusitis, but there is growing literature promoting honey as an antimicrobial and antiinflammatory agent.[2] This is the first documented use for those suffering from sinusitis. However, honey has been used as medicine by the Greeks and Egyptians since ancient times and is now being used for a wide variety of wound care.[3] The manuka honey used in this project is called Medihoney, which is a licensed medical device with well-documented antimicrobial properties.[3–6] If manuka honey is effective in reducing the mucosal infection and inflammation seen in postoperative patients who continue to suffer from AFRS, then there may be advantages to its use in those who continue to fail medical and surgical management.

Materials and Methods

This study was a randomized, single-blind, prospective study and was approved by the University of British Columbia's ethical review board. Patients included in the study had undergone bilateral functional endoscopic sinus surgery (FESS) and had a definitive diagnosis of AFRS prior to consideration for the study. Modified diagnostic criteria are used for AFRS at our centre, and patients are required to have all five characteristics to be diagnosed with AFRS (see Table 1). They had to have failed standard medical treatment (budesonide irrigations) for at least 12 weeks post-FESS and have tried a course of systemic antifungals and steroids. All patients were 19 years of age or older. Patients allergic to pollen, honey, or bees were prohibited from participating in the study.

The rigid endoscope was used to assess the mucosal inflammation. The mucosa was graded by a staging system used in our clinic. Each sinus cavity (frontal, ethmoid, maxillary, and sphenoid) was given a score between 0 and 9, with an extra point for the presence of fungal mucin, giving a total potential maximum score of 40 per side (Table 2).[7] This endoscopic grading system, which has

Table 1. Diagnostic Criteria for AFRS, including St. Paul's Sinus Centre Modification

1. Type 1 hypersensitivity confirmed by history, skin tests, or serology
2. Nasal polyposis
3. Characteristic CT scan (double-density sign)
4. Eosinophilic mucus without fungal invasion into sinus tissue
5. Positive fungal stain of sinus contents removed intraoperatively or during office endoscopy
6. Immunocompetence (replaces no. 1 at St. Paul's Sinus Centre)

AFRS = allergic fungal rhinosinusitis; CT = computed tomographic.

Table 2. Philpott-Javer Endoscopic Scoring System

Sinus Cavity	*Right*	*Mucin*	*Left*	*Mucin*
Frontal	0–9	1	0–9	1
Ethmoid	0–9	1	0–9	1
Maxillary	0–9	1	0–9	1
Sphenoid	0–9	1	0–9	1
Total	40	40		
Bilateral total	80			

Grading: 0 = no edema; 1–3 = mucosal edema (mild/moderate/severe); 4–6 = polypoid edema (mild/moderate/severe); 7–9 = frank polyps (mild/moderate/severe).

been sent for peer review, allows clinicians to closely follow each sinus cavity between each visit and compare the severity of the disease. In this grading system, if the frontal sinuses are not visible, then the frontal recesses are used. For patients who fit the inclusion criteria for the study, the senior author (A.J.) stepped out of the room and a closed envelope system was used to randomly pick which nostril would receive the honey treatment. Patients acted as their own control. In other words, the patients continued with their current medical management in both nostrils, but only one nasal cavity was selected to undergo honey treatment. At this time, microbiology samples were taken from both ethmoid cavities with swabs via the endoscope and sent to the laboratory for cultures and sensitivity testing.

Patients were instructed to spray 2 mL of 50/50 honey-saline solution using a mucosal atomization device in their selected nostril once a day at night for 30 days. Patients who were using budesonide irrigations or any other form of medical management (ie, saline rinse) were instructed to use this prior to spraying the honey. Patients were seen after 30 days, and the senior author, who was blinded, assessed both nostrils and determined which nasal mucosa looked healthier using our endoscopic mucosal grading system. Patients filled out a validated survey (Sino-Nasal Outcome Test [SNOT-22]) regarding their nasal symptoms during their initial visit and after 4 weeks of treatment.

The honey used in the study is formally known as Medihoney, with active *Leptospermum* honey (Device ID: 241269; LN: 74159). The honey was obtained from Derma Sciences Inc (Toronto, ON) for research purposes. There were no competing interests.

To obtain a significant result with a power of 80% ($p < .05$), at least 31 patients with AFRS were required to detect a benefit from the treatment. An improvement in the endoscopic mucosal score of 5 or more points was considered significant. Paired *t*-tests were used to compare the mucosal and SNOT-22 scores using *Stata* software (StataCorp, College Station, TX).

Results

Thirty-eight patients were enrolled in the study. Four patients did not complete the course of treatment, of whom only one did not complete the study owing to side effects. This patient experienced nausea on douching with the honey solution. No other systemic side effects were experienced. Three patients complained of tolerable burning sensation within their nasal mucosa but were able to finish their course of treatment.

An improvement in the endoscopic mucosal score of 5 or more points was considered significant. Table 3 illustrates the results of all patients enrolled in the study. We retrospectively determined their AFRS subtype by looking up their IgE levels and clinically reported mucin findings. Table 4 shows the results of comparing the mucosal score at outcome showing that the treatment group had a mean score −1.74 units different from the control group (95% CI −5.02 to 1.55), but this was not statistically significant ($p = .2901$).

Qualitative analysis of the microbiology results revealed no consistent trends. Patients grew a varying range of bacterial flora, with no obvious response to the honey treatment. Of the 34 patients who completed the study, 20 individuals had complete pre- and posttreatment surveys (Table 5). A significant subjective improvement was appreciated ($p = .0220$).

Discussion

Patients with AFRS tend to suffer from anterior and/or posterior mucopurulent drainage, nasal obstruction, facial pain or pressure, and a decreased sense of smell. Patients tend to have at least two of these symptoms, which can lead to a very debilitating life. AFRS may be a subtype of chronic rhinosinusitis, but the propensity for the disease to rapidly return makes the condition much harder to treat effectively. Although the criteria and pathophysiologic factors are disputable, what is irrefutable is that these patients have a distinct clinical pattern of recurrent nasal polyposis and accumulation of "allergic" mucin. There is certainly heterogeneity among this group of patients, who may or may not have elevated IgE levels (and may even have IgE specific to certain fungi), may or may not have asthma, and may or may not have a specific IgG deficiency.

Table 3. Cumulative Results

Patient	AFRS Subtype	Pre-treatment Mucosal Score	Posttreatment Mucosal Score	Precontrol Mucosal Score	Postcontrol Mucosal Score	Change in Treated Mucosa Score	Change in Control Mucosa Score	Response to Honey Treatment
1	EMRS	28	26	30	22	−2	−8	Worse
2	EFRS	12	2	26	27	−10	1	Yes
3	EMRS	20	27	21	21	7	0	Worse
4	EMRS	19	6	11	30	−13	19	Yes
5	AFRS	25	12	25	27	−13	2	Yes
6	AFRS	17	14	16	7	−3	−9	Worse
7	EMRS	32	33	28	23	1	−5	Worse
8	EMRS	27	27	26	18	0	−8	Worse
9	Unknown	12	6	11	17	−6	6	Yes
10	AFRS	36	18	32	13	−18	−19	No impact
11	EMRS	21	25	23	24	4	1	No impact
12	Unknown	5	15	4	7	10	3	Worse
13	EMRS	16	10	20	15	−6	−5	No impact
14	EMRS	3	9	1	13	6	12	Yes
15	EMRS	17	23	9	17	6	8	No impact
16	EFRS	16	20	10	24	4	14	Yes
17	EMRS	33	38	25	38	5	13	Yes
18	EFRS	12	8	9	30	−4	21	Yes
19	EFRS	10	13	10	13	3	3	No impact
20	AFRS	13	8	13	9	−5	−4	No impact
21	AFRS	34	36	34	36	2	2	No impact
22	EFRS	12	12	4	2	0	−2	No impact
23	EFRS	37	28	37	30	−9	−7	No impact
24	AFRS	20	10	35	23	−10	−12	No impact
25	AFRS	12	7	15	8	−5	−7	No impact
26	EFRS	22	13	27	24	−9	−3	Yes
27	Unknown	19	20	19	21	1	2	No impact
28	EMRS	26	30	26	25	4	−1	Worse
29	AFRS	22	5	28	6	−17	−22	No impact
30	Unknown	22	23	16	16	1	0	No impact
31	EMRS	14	15	15	16	1	1	No impact
32	EMRS	20	22	22	16	2	−6	Worse
33	EMRS	25	23	26	21	−2	−5	No impact
34	AFRS	15	1	15	5	−14	−10	No impact

AFRS = allergic fungal rhinosinusitis; EFRS = eosinophilic fungal rhinosinusitis; EMRS = eosinophilic mucin rhinosinusitis.

Table 4. Outcome Summary Statistics

	Control	*Treatment*		
	Mean (SD)	*Mean (SD)*	*Difference (95% CI)*	p *Value**
Mucosal score	18.94 (8.92)	17.21 (9.90)	−1.74 (−5.02 to 1.55)	.2901
Change in mucosal score	−0.74 (9.48)	−2.62 (7.27)	−1.88 (−5.04 to 1.27)	.2334

*Based on a paired *t*-test.

Table 5. SNOT-22 Scores

Patient	*SNOT-22 Before*	*SNOT-22 After*	*Difference in Score*
1	45	41	4
2	26	29	−3
3	23	26	−3
5	60	56	4
6	10	4	6
8	38	42	−4
9	96	80	16
10	56	35	21
11	52	24	28
14	31	6	25
17	52	50	2
18	53	47	6
20	15	4	11
21	47	37	10
23	82	76	6
25	28	25	3
27	7	34	−27
30	54	17	37
31	17	9	8
33	51	49	2

SNOT-22 = Sino-Nasal Outcome Test.

The goal in treating AFRS is to reduce mucosal edema, promote sinus drainage, and eradicate infections that might be present. Patients are often given topical or oral steroids, antifungals, immunotherapy, or nasal irrigation, and if medical managment fails, they undergo FESS. However, patients can still suffer from AFRS after all medical and surgical options have been exhausted. Few options are left for those who continue to suffer. We considered honey as a possible alternative given its remarkable results in healing wounds.[8–11] The healing that is necessary in a sinus cavity for sinusitis is very similar to the process that takes place when treating relcalcitrant surgical wounds with honey.[10] The most widely used honey comes from New Zealand and Australia from bees that feed on the *Leptospermum scoparium* bush. The medical honey used in our clinical experience was Medihoney, which comes from an assortment of *Leptospermum* species honeys.

The honey's mechanism to act as an antimicrobial and antiinflammatory agent is multifactorial. Its ability to act as an antimicrobial agent is due to the acidic pH and osmotic effect of the honey, as well as the glucose oxidase and hydrogren peroxide content.[3–6] The hydrogen peroxide also plays a key role as an antiinflammatory agent.[12,13] Moreover, the glucose in honey provides energy to vital cells such as phagocytes, which are in dire need of energy production in areas where oxygen supply is often deficient.[2] Nevertheless, what makes manuka honey different from other honeys is a property known as unique manuka factor (UMF), the active ingredient of which is unknown. Honey with UMF continues to have antimicrobial activity even when the hydrogen peroxide is eliminated.[3] Given all of these properties, manuka honey provides very good microbial coverage.

Unfortunately, this initial study did not show any significance in the treatment of AFRS with manuka honey. Given the uncharted territory of using honey in the sinuses, we were cautious with respect to the amount and how often the honey was administered. A subjective decision was made to use 2 mL of a 50% (vol/vol) mixture of honey-saline solution to treat the chronic infection and inflammation as it was felt that the mixture was potent enough to maintain its antimicrobial and antiinflammatory activity as well as fluid enough to allow for optimal ciliary function in the sinuses. It has been shown that concentrations below 10% have had therapeutic significance.[14] Unfortunately, our results were inconclusive as to whether the 50% solution showed antiinflammatory and antimicrobial activity with 30 days of treatment. It is unknown whether a longer treatment course would have shown more positive results. On the other hand, close analysis of the data showed that the treated side of a number of patients responded extremely well compared to the control side. It is difficult to conclude what factors resulted in these positive results. A number of the patients who responded well had high IgE levels, which suggests that a particular subtype of AFRS may be suitable for honey treatment. The honey treatment also gave patients a general sense of improvement, which was shown by the significant improvement in SNOT-22 scores ($p = .0220$). Given that honey is an organic product, it may provide a therapeutic psychological benefit for those who have failed multiple conventional treatments.

As for any stated side effects from honey administration, four patients complained of a burning sensation within the sinus cavity. The producers of the honey state that this burning sensation is a documented side effect of manuka honey and is believed to occur when the patient's tissue is undergoing an inflammatory phase. Nevertheless, all four patients were compliant with their honey treatment and were able to continue with the study. On the other hand, one patient documented nausea after spraying the honey and consequently became noncompliant with the study.

Manuka honey is well known for its antimicrobial and antiinflammatory components, but our study design did not show its effectiveness in treating AFRS. Given the extensive research on manuka honey and the positive impact on recalcitrant wounds, further research is warranted in this field to determine the optimal honey concentration, drug delivery, and how often honey should be applied to the sinuses.

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