

**EFFICACY OF HONEY NASAL SPRAY AS AN
ADJUNCT TREATMENT FOR ALLERGIC RHINITIS:
A RANDOMIZED CONTROLLED TRIAL**

BY

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1.1 INTRODUCTION

Allergic rhinitis (AR) is the most common form of non-infectious rhinitis defined by an allergen-induced IgE-mediated inflammation of the nasal mucosa.¹ Thought to occur after exposure to indoor and outdoor allergens such as house dust mite, insects, animal dander, molds and pollen. Patients usually presented with cardinal symptoms of rhinorrhea, sneezing, nasal itchiness and nasal blockage. AR involved in the cascade of inflammatory reaction whereby the initial exposure to allergens will produce an early response within minutes. At this phase, inflammatory mediators will cause mucosa edema leads to nasal congestion, rhinorrhea and also stimulation of sensory nerve cause reflexes sneezing. The late phase response occurs after 4-8 hours of exposure to allergens. The cells mediated inflammatory reaction will be activated and nasal congestion will be prominent at this stage. Cytokines produce during this phase can be reduced by glucocorticoids.

AR can be classified according to its duration and severity. Persistent AR is when the patient experience symptoms at least 4 days a week and for at least 4 weeks while intermittent AR is when the symptoms are present less than 4 days a week or for less than 4 weeks. According to severity it can be divided into mild and moderate-severe. In mild AR, none of these criteria of sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work or troublesome symptoms while in moderate to severe AR, at least 1 of the criteria present.²

The prevalence of AR is about 10-20% of the population. In Malaysia, about 20-48.9% of patients suffering from moderate to severe persistent allergic rhinitis.³

Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines have been widely used to treat approximately 500 million affected patients globally.

According to this guideline, the mainstay treatment for moderate to severe persistent AR are intranasal corticosteroid and oral antihistamine. Pharmacologically, intranasal corticosteroids act by binding to endogenous corticosteroids receptors that involved in the inflammatory process, thus increase the synthesis of anti-inflammatory mediators and reduce the synthesis of proinflammatory mediators. It is effective against all symptoms of AR. Meanwhile, oral H1-antihistamines acts by blocking the histamine receptors and are effective against symptoms mediated by histamine (rhinorrhea, sneezing, nasal itching and eye symptoms) but are less effective for nasal congestion.

As compared to oral antihistamine, intranasal corticosteroids are more effective in view of high local drug concentration and minimal systemic bioavailability.⁴

Few studies have been done to complement this standard treatment to improve management of AR in term of quality of life as well as economically.^{5,12}

However, none of the study used honey in the form of nasal spray for alternative treatment of AR. Honey nasal spray is the best way of administration to achieve the higher local effect. Thus, this study is conducted with the aim to assess the efficacy of Tualang honey nasal spray as adjunctive treatment of moderate to severe AR.

Honey has been widely used as a food supplement as well as natural remedies since ancient time. The composition as well as physical properties of each honey will be differ according to the botanical and geographical origin. Various studies have been done to analyse the physiochemical properties of various types of honey in Malaysia and amongst them, Tualang

honey has a higher phenolic and flavonoid content that possesses the antioxidant properties.

6,7,8

A review article by Vallianouet *et al*, General Med, 2014 on honey showed that anti-inflammatory and antioxidant properties of honey is from its bioactive substances of phenol and flavonoids.⁹ Among various types of Malaysian honey, Tualang honey has been shown to have high phenolic.¹⁰

The anti-inflammatory effect of Tualang honey has been studied by Kamaruzaman *et al*. They investigated the effect of aerosolized honey (25% and 50% diluted) as an agent to alleviate the asthma-related histopathological changes that occur in the rabbit airway following ovalbumin (OVA)-induce airway inflammation. They demonstrated that treatment of aerosolized honey is effectively inhibited (OVA)-induced airway inflammation by alleviating asthma-related histopathological changes in the airway and also prevented occurrence of asthma.¹¹

Another study done by Zamzil Amin et al, comparing the outcome between placebo and ingestion of honey to improve the symptoms of allergic rhinitis found that there are significant improvements in 4 cardinal symptoms of AR in patients who ingested honey and the improvement persist for 1 month after cessation of the treatment.¹²

Farnaz Hashemaian and colleagues from Hamadan University of Medical Science, Iran, did a study on effect of thyme honey nasal spray on chronic rhinosinusitis. It is a double-blind randomized controlled clinical trial comparing the outcome of treatment of post FESS patients with thyme honey nasal spray and placebo as adjunct to fluticasone nasal spray. They found

that trial group who received honey nasal spray showed significant improvement decrease in endoscopic scores as compared to those received placebo as an adjunct.¹³

Beside its anti- inflammatory properties, Tualang honey also has antibacterial effect. Nasir et al found that tualang honey has bacteriostatic and bactericidal effects and can be use as dressing for burn wound.¹⁵

2.0 STUDY OBJECTIVES

2.1 General objectives

To evaluate the effectiveness of honey nasal spray as an adjunct treatment in patient with moderate to severe persistent allergic rhinitis.

2.1 Specific objectives

- 1.** To evaluate the mean total SNOT-22 score between control and trial group at baseline, 2nd and 6th weeks of treatment.
- 2.** To evaluate the mean symptoms score (rhinorrhea, nasal blockage & sneezing) between control and trial group at baseline, 2nd and 6th weeks of treatment.
- 3.** To evaluate the total serum IgE level between control and trial group at baseline and 6th weeks of treatment.

3.1 TITLE : EFFICACY OF TOPICAL HONEY NASAL SPRAY AS AN ADJUNCT TREATMENT FOR ALLERGIC RHINITIS

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3.2 ABSTRACT

BACKGROUND

Allergic rhinitis is an IgE-mediated inflammation of the nasal mucosa. The management of allergic rhinitis has not changed much and only limited studies has been done to explore the benefit of complementary alternative therapy. Honey is proven in its anti-inflammatory, anti-bacterial and anti-oxidant properties and found to be useful for treatment of inflammation. We aimed to determine the efficacy of honey nasal spray as an adjunct treatment of moderate to severe persistent allergic rhinitis.

METHOD

Patients were recruited from our Otorhinolaryngology- Head & Neck Surgery Clinic from November 2015 to July 2016. Thirty moderate to severe persistent allergic rhinitis patients with positive skin prick tests were divided randomly into control and trial group. Both groups received standard medication (intranasal corticosteroids and oral antihistamines). In addition, the trial group received honey nasal spray as adjunctive daily dose. Patients were assessed

using SNOT22 questionnaires at 0, 2nd and 6th weeks of the study with the focus on the primary symptoms of nasal blockage, rhinorrhea and sneezing

RESULTS

There was overall improvement of total SNOT 22 score and each symptom score of nasal blockage, rhinorrhea and sneezing together with the total serum IgE level in both groups at the end of 6 weeks. However, the improvement was seen more consistently in the trial group as evidenced by the reduction of estimated means score of all measured outcomes.

CONCLUSION

The honey nasal spray has beneficial effect as an adjunct treatment in moderate to severe persistent allergic rhinitis by acting as a protective mucous layer in reducing the attachment of allergen to the nasal mucosa.

Keywords: Honey; Topical nasal spray; Allergic rhinitis

3.3 INTRODUCTION

Allergies in Asia-Pacific Survey found that the overall prevalence of allergic rhinitis (AR) among Asian was 8.7%.¹ This will continue to increase in view of rapid economic development and urbanization. Asha'ari et al² found that 20-48.9% of patients suffering from moderate to severe persistent AR in Malaysia. In patients with AR, exposure to allergens will produce an early response within minutes which results in a cascade of inflammatory reaction. Inflammatory mediators will cause mucosa edema that leads to nasal congestion, rhinorhea and also stimulation of sensory nerve which causes reflex sneezing. The late phase response occurs after four to eight hours of exposure to allergens. The cells mediated inflammatory reaction will be activated and nasal congestion will be prominent at this stage.³

As proposed by ARIA guidelines 2007, the standard treatment for moderate to severe persistent AR are intranasal corticosteroids (INS) and oral antihistamine.⁴ Both acts by reducing the inflammatory reaction in AR. From our observation, we found that, many of our patients were dependent on the medications despite compliant because we cannot step down the medications. This probably due to continuous allergen exposure.

With prolonged use of intranasal corticosteroid, the patients are more concerned on its side effects. Growth retardation, thinning of the skin and osteoporosis is the well known systemic side effects of steroid. Even though intranasal corticosteroid has lower systemic bioavailability as compare to inhaled corticosteroid, systemic side effect such as suppression of hypothalamic-pituitary axis (HPA) and growth retardation has been reported in children with prolonged use of INS.⁵ However, local side effects are commonly experienced by patients who received long term INS such as epistaxis, dryness and crusting of the nasal mucosa.⁶

Oral antihistamine meanwhile, has its systemic side effect which is contributed by its sedative action, such as drowsiness and CNS depressant. Other than that, it also has a relative risk of cardiotoxicity.⁷ The sedative effect might impair patient's school and work performance as well as quality of life.

Concerned with the above matter, we conducted a study on topical use of honey in allergic rhinitis to minimize the treatment of AR.

Honey has an anti-inflammatory property and is widely used in studies conducted to complement the conventional treatment in AR. However, at which level of inflammatory processes that is blocked by honey is unknown. Honey also has been recognized to have immunomodulatory property and the anti allergic effect might be due to this component.⁸

Although, many studies had been conducted to complement the conventional treatment in AR, all of these studies used different type of honey and different routes of administration.^{9,10} This is the first study to the best of our knowledge that use tualang honey in the form of nasal spray.

3.5 METHODOLOGY

Study subjects

The study protocol was approved by Medical Research and Ethic Committee of National Medical Research Registry (NMRR) Malaysia [NMRR-1-987-25579 (IIR)]. Patients were recruited from our Otolaryngology- Head & Neck Surgery clinic from November 2015 until July 2016. Those who were 18 years old and above, moderate to severe persistent AR with positive skin prick test (SPT) were included in the study. Patients with known allergy to honey, with multiple comorbid conditions such as chronic obstructive pulmonary disease, diabetes

mellitus and ischaemic heart disease as well as those who were pregnant and had undergone nasal surgery before were excluded. The patients' demographic data and clinical history were recorded in the patient's profoma. All patients underwent skin prick test (SPT) using ALK-Abello skin prick test kit. They were tested for 11 allergens with positive and negative control. The allergens were *Blomia tropicalis* (house dust mite), *Dermatophagoides pteronyssinus* (house dust mite), *Dermatophagoides farinae* (house dust mite), *Felis domesticus* (cat), chicken meat, shrimp, egg white, egg yolk, cow's milk, peanut, *Apis mellefera* (honey bee), histamine (positive control), saline solution (negative control). SPT is positive in the presence of wheal of 2 mm more than negative control after 15 minutes.

Study design and randomization

This was a randomized control trial study. With simple randomization technique, 15 subjects were enrolled in each control and trial groups. During randomization, the patients were given 1 sealed envelope with a piece of paper written number 1 or 2. Those who received number 1 were recruited into a control group and number 2 were trial group.

Study intervention

According to ARIA guidelines, all patients were already treated with standard treatment which were topical intranasal corticosteroid two puffs daily and oral antihistamine 10 mg daily. The trial group received additional adjunctive topical honey nasal spray 2 puffs at night. The treatment duration was for 6 weeks. The correct nasal spray technique was taught at the beginning of the study. They were instructed to use intranasal corticosteroid in the morning and honey nasal spray at night. Trial subjects were given a product brochure which consists of

brief information of topical honey nasal spray, its content and indication as well as usage and storage instructions. To ensure compliance, a diary to record date using honey nasal spray and any side effects were given.

Interventional product

The honey nasal spray was prepared in a laboratory at AMDI, Bertam. The source of tualang honey is from Federal Agricultural Marketing Authority (FAMA), Ministry of Agriculture & Agro-Based Industry Malaysia. Few processes involved in the production of honey nasal spray such as the formulation are sterilized using filter unit, which remove traces of fine particles in the solution. Seventy five percent of honey is mixed in sterile distilled water. Subsequently, the PET bottles were exposed to UV-light for at least 2 hours, in order to disinfect the microorganisms on the surface of the bottles. Once the sterilization process is done, the filtered-honey is aliquot into the bottles and ready to be distributed to patients (Figure 1).



Figure 1: Honey nasal spray in 120 millilitre PET bottle.

Evaluation

The symptoms were evaluated using a validated Malay-version Sinonasal Outcome Test-22 (SNOT-22) questionnaire. The score was recorded at the beginning of the study (week 0) and repeated at the 2nd and 6th weeks of the study. Out of 22 questions, we highlighted the total score and 3 most common symptoms in AR which were nasal blockage, rhinorrhea and sneezing. The scoring is done by asking the subjects to rate the severity of symptoms with Linkert scale of five where 1 (means no problem) to 5 (means the most problematic). In addition, total serum IgE levels were done for all patients to objectively measure the outcome. Blood was taken for total serum IgE at the beginning (week 0) and at the end of the study (week 6).

Data analysis

All the measured outcomes were analysed using repeated measure ANOVA to determine the significance of differences in total symptoms score and individual symptoms score between control and trial group at 0, 2nd and 6th week of study.

3.5 RESULT

Thirty AR patients were recruited in this study. All were classified as moderate to severe persistent AR according to ARIA guideline and had a positive skin prick test to aeroallergens. They were randomly and equally divided into control and trial group. The mean age of patients was 32.2 years with an average of 33.7 years old for control and 30.8 years old for trial group. Eighteen were female, 10 of them were in trial group. The majority of the patient population were Malay (80%) followed by Chinese (16%) and Indian (4%).

Repeated measured ANOVA was done to evaluate the measured outcome between each group at baseline, 2nd and 6th weeks of the study period. All scores in the SNOT-22 questionnaire were measured using survey score of Linkert scale of five whereby 1 (means no problem) to 5 (means the most problematic). Out of 3 nasal symptoms that we assessed, nasal blockage is the most common complaint with mean score 3, followed by sneezing (mean score 2.9) and rhinorrhea (mean score 2.8).

Table 1 shows significant improvement seen in mean symptoms score of all measured outcomes at the end of the study. In both groups, rhinorrhea showed early significant improvement (by 2nd week) meanwhile sneezing showed improvement only at the end of the study. At the end of the study, there was an improvement of the mean total symptom score as well as the total serum IgE level in both control and trial groups. However, when comparing the overall mean score in between control and trial groups, there was no significant difference observed. This suggests that both groups had improvement of symptoms after treatment either with standard treatment only or with adjunctive honey nasal spray (Table 2).

Table 3 shows that both groups had improvement of estimated marginal means score of all parameters at the end of study and the improvement seen more in rhinorrhea and sneezing parameter as demonstrate by positive mean different (MD).

Table 1. Comparison of the improvement of the mean symptom score of the 3 symptoms of AR, Total SNOT-22 score and total serum IgE level in control and trial groups (based on time effect).

Symptoms	Week	Control		Trial	
		mean difference (95% CI)	p-value	mean difference (95% CI)	p-value
Nasal blockage	0-6	1.33 (0.55, 2.11)	0.001	1.53 (0.41, 2.65)	0.007
Rhinorrhea	0-6	1.00 (0.47,1.53)	0.000	1.33(0.28, 2.38)	0.012
Sneezing	0-6	1.07 (0.57,1.56)	<0.001	1.67 (0.55, 2.78)	0.030
Total SNOT-22	0-6	9.73 (1.51, 17.96)	0.019	17.40 (3.59, 31.21)	0.012
Total serum IgE	0-6	33.59(5.77,61.40)	0.021	103.58(7.13,200.03)	0.037

Table 2. Comparison of mean difference of symptom score and total serum IgE level between control and trial groups at 6th week.

Symptoms	Comparison	Mean difference (95% CI)	p-value
Nasal blockage	control-trial	-0.11 (-1.14, 0.91)	0.826
Rhinorrhea	control-trial	0.40 (-0.47,1.27)	0.356

Sneezing	control-trial	0.31(-0.41, 1.03)	0.383
Total SNOT-22	control-trial	-11.84 (-27.68, 3.99)	0.137
Total serum IgE	control-trial	-171.097 (-440.357, 98.164)	0.204

Table 3 : Comparison of score among control and trial groups based on time (Time-treatment interaction)

Symptoms	Time	Comparison	Mean	Mean different (95% CI)	p-value
Nasal blockage	0 weeks	Control	2.93	-0.133	0.834
		Trial	3.07	(-1.143,1.16)	
	2 nd weeks	Control	2.07	-0.27	0.628
		Trial	2.33	(-1.38,0.85)	
	6 th weeks	Control	1.60	0.07	0.894
		Trial	1.53	(-0.95,1.08)	
Rhinorrhea	0 weeks	Control	2.53	-0.53	0.257
		Trial	3.07	(-1.48,0.41)	
	2 nd weeks	Control	1.80	-0.47	0.290
		Trial	2.27	(-1.35,0.42)	
	6 th weeks	Control	1.50	-0.20	0.703
		Trial	1.73	(-1.26,0.86)	
Sneezing	0 weeks	Control	2.67	-0.53	0.207
		Trial	3.20	(-1.38,0.31)	

	2 nd weeks	Control	2.00	-0.47	0.346	
		Trial	2.47	(-1.46,0.53)		
	6 th weeks	Control	1.60	0.067	0.872	
		Trial	1.53	(-0.77,0.91)		
Total SNOT-22	0 weeks	Control	29.93	-15.40	0.079	
		Trial	45.33	(32.69,1.89)		
	2 nd weeks	Control	24.33	-12.40	0.144	
		Trial	36.73	(-29.29,4.49)		
	6 th weeks	Control	20.20	-7.73	0.346	
		Trial	27.93	(-24.26,8.79)		
	Serum IgE	0 weeks	Control	285.97	-206.09	0.163
			Trial	492.06	(501.02,88.83)	
6 th weeks		Control	252.38	-136.10	0.275	
		Trial	388.48	(-386.34,114.14)		

3.6 DISCUSSION

Sinonasal Outcome Test-22 (SNOT-22) questionnaire is an assessment tool commonly used to evaluate the quality of life in patients with chronic rhinosinusitis. The SNOT-22 questionnaire has the advantage of combining issues which are specific of sinonasal disease with general health issues, which may be assessed alone or together.¹¹ In addition, it also has been shown to be an accurate assessment tool in the evaluation of patients with allergic rhinitis.¹² As all of our patients communicate using Malay language, we use the Malay validated Sinonasal Outcome Test-22 (SNOT-22) questionnaire in our study in order to give an accurate assessment of the treatment outcome.¹³ We focus on the three most common symptoms in AR which were nasal blockage, rhinorrhea and sneezing as these symptoms have been shown to be the most troublesome among allergic rhinitis sufferers.¹⁴

Our study showed significant improvement of total symptoms score and total serum Ig E level in both groups. However, trial group who received honey nasal spray exhibited more consistent alleviation of symptoms (nasal blockage, sneezing and rhinorrhoea) as well as reduction in total serum Ig E level as shown by the estimated means total symptoms score throughout the study period from week 0 to week 6. This demonstrates that the tualang honey nasal spray has adjunctive beneficial effect in alleviating the symptoms of AR. The exact mechanism of action (MOA) of honey is not yet known. The anti-inflammatory and antioxidant properties of honey most probably due to its bioactive substances of phenol and flavonoids.¹⁵ Mohamed et al.¹⁶ have shown that Malaysian Tualang honey contains highly phenolic and flavonoid compounds that possess relatively good antioxidant activity. Flavonoid exert its anti-inflammatory effect by its action on the enzymes (kinase and thyrosine) involved in the inflammatory processes. It competitively binds to ATP at catalytic sites of the enzymes, thus leads to inactivation of signal transduction in the immune cascade.¹⁷ The anti-inflammatory effect of honey was well

demonstrated by Kamaruzzaman et al.¹⁸ This study uses aerosolized tualang honey to treat ovalbumin induce asthma in rabbits. Histopathological examinations of rabbit lungs showed reduction in the mucus secreting goblet cell hyperplasia of respiratory epithelium after 5 days of honey nebulizer.

The more consistent reduction in total serum IgE level in trial group as compared to the control group (showing a slight increase in estimated marginal mean at 6th week) demonstrates the anti allergic property of honey. Ishikawa et al¹⁹ found that honey bee exert an anti-allergic effect by inhibiting the Fc immune-globulin E receptor that inhibits binding of IgE to mast cell and thus prevents mast cell degranulation.

The other possible mechanism of action of tualang honey is directly by its local effect on the nasal mucosa. Thick and sticky consistency of tualang honey will form a layer acting as mucosal barrier in preventing the attachment of aero-allergens to the nasal mucosa. Thus, this will reduce inflammatory reactions by reducing the number of allergens being presented to the antigen representing cells (APC). This is the most probable reason for the symptoms reduction seen in our patients who received the topical honey nasal spray.

Since ancient time, honey has been widely used as food supplement and natural remedies for various chronic illnesses. Due to its beneficial effect on various diseases, the disadvantage of honey either by ingestion, inhalation or topical use is less debated. The only myths on the disadvantages or limitation of honey is its use in diabetics. Most believed that it can worsen blood sugar level in diabetics. However, the study showed that honey, especially tualang, has intermediate glycemic index and help in reducing blood sugar level when use in combination with oral hypoglycemic agents.^{20,21}

Pharmacologically, oral ingestion of honey has more systemic bioavailability and causes more systemic effect. Vice versa in our study, whereby we found that, a significant reduction of the total serum IgE level at the end of study in trial group. The clinical improvement of nasal symptoms, however, are less significant. This is the uniqueness of honey and we postulated that topical honey in this study exerts more systemic effects. The possible mechanism of action probably by absorption from nasal mucosa. However, the exact MOA is still not well understood and beyond this study.

Apart from its systemic beneficial effect, topical honey does have local side effect mainly local discomfort and excessive rhinorrhea immediately after use.

The study is not without limitations. It is a single centre study and the small sample size may not represent the whole population. As this study is only for short duration, the long term effect of the topical honey nasal spray as well as any residual effect after its discontinuation remained to be seen. It is a possibility that there might be more consistent reduction in total symptoms score and IgE level by the continuous use of honey nasal spray and a longer duration of study is warranted to determine its long term efficacy.

Conclusions

The topical honey nasal spray has beneficial effect as an adjunct treatment in moderate to severe persistent allergic rhinitis by acting as a protective mucous layer in reducing the attachment of allergens to the nasal mucosa. The anti-inflammatory and anti-allergy property is yet to be proven and requires further study.

All authors declared no conflict of interest.

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- (2) drafting of the article or critical revision of the article for important intellectual content; and
- (3) final approval of the version to be submitted.

When authorship is attributed to a group, all authors must meet the listed criteria and must be responsible for the quality, accuracy, and ethics of the work. All authors must participate in determining the order of authorship.

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For submission to *AP Allergy*, studies on human beings must comply with the principles of the Declaration of Helsinki and its recommendations guiding physicians in biomedical research involving human subjects (adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; the 35th

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