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HONEY IN THE TREATMENT OF PERSISTENT CHRONIC OTITIS EXTERNA; A RANDOMIZED PLACEBO-CONTROLLED TRIAL

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ABSTRACT

Background: The current study aimed to determine the efficacy and safety of honey in the treatment of persistent chronic otitis externa. **Patients and methods:** This randomized-controlled study was conducted in Helwan and Banha Medical Universities Hospitals, Egypt in the period 2014-2016. Eligible patients were randomly allocated to the study group and the control group. For the study group, Honey ear drops 1 ml was used, and for the control group undiluted glycerol was used. The primary outcome measure was the number of organisms in tenfold diluted broth culture in after the treatment period. **Results:** A Hundred patients were included in the analysis, 50 in each group. The two groups were comparable regarding the baseline characteristics. At the end of the study, there was a highly significant difference in the number of organisms in tenfold diluted broth culture between groups (p-value < 0.001) where it was 34.28(9.37) & 58.98 (11.44) in the Honey groups and the Placebo group, respectively. Moreover, improvements in patients' symptoms (discomfort, itchiness, wetness, and smell) were significantly higher in the Honey group than in the Placebo group. Also, improvements of signs (erythema, ulceration, granulation and discharge quantity) were significantly higher in the Honey group than in the Placebo group. There were no adverse events for the Honey drops. **Conclusions:** Honey is effective as ear drops for persistent chronic otitis externa.

KEYWORDS: Honey; ear drops; persistent otitis externa; otorrhea.

INTRODUCTION

Throughout the history of humanity, in addition to its widespread utilization as a popular food, honey has been extensively used as a healing agent. It is a bee-derived, supersaturated solution composed mainly of fructose and glucose, and also contains proteins and amino acids, enzymes, minerals, and vitamins.[1,2]

Honey also has a very beneficial role attributed to its antibacterial, antiviral, and antifungal features that result from its high acidity, osmolarity, and content of hydrogen peroxide and non-peroxide components like methylglyoxal.[3,4]

Hydrogen peroxide is predominantly the antimicrobial agents in honey, and its concentration is regulated by glucose oxidase and catalase levels.[3,5] In addition, some types of honey contain levels of bee defensin-1 that is bacteriostatic, fungistatic and inhibits the growth of enveloped viruses.[6,7]

These antimicrobial features are crucial in the management of the dermatological diseases. It is particularly appropriate as a dressing for wounds and burns. Also, it has also been used in the treatment of psoriasis, seborrhea, dandruff, pityriasis, tinea, diaper dermatitis, hemorrhoids, and anal fissure. Moreover, it has been used in cosmetic formulations because it has an emollient, soothing, humectant, and hair conditioning effects. Besides, it retards the formation of wrinkles, keeps the skin juvenile, regulates the pH and prevents infections.[2]

To the best of our knowledge that Henatsch et al. (2017) presented a proof-of-concept study for the treatment of the recurrent eczematous otitis externa with Honey in a prospective preliminary case series study which indicates a possible role of honey eardrops in eczematous ear disease.[8]

Chronic otitis externa (COE) remains a frustrating problem for both patient and physician. It is a chronic inflammation of the skin lining the external ear canal leading to the eardrum. The causes behind COE include microbial etiology like a bacterial or fungal infection. Other causes are eczema or seborrhea, chronic irritation, allergy or nervous habit of frequently scratching the ear.[9]

Therefore, in the current randomized placebo-controlled study, we aimed to determine the effectiveness and safety of honey in the treatment of persistent chronic otitis externa.

Patients and Methods

This prospective parallel randomized controlled trial was conducted in Banha and Helwan Universities hospitals, Egypt, during the period from February 2014 to March 2016. This study followed the principles of the Declaration of Helsinki and following the Medical Research Involving Human Subjects Act (WMO), and was approved by Institutional Review Board. The purpose of this study was clearly explained in the Arabic language to all parents of the subjects before their enrolment to the study, and an informed consent form was signed by and obtained from all of those enrolled.

We recruited male and female patients with age from 18-55 years old attending Banha and Helwan Universities hospitals Egypt having persistent chronic otitis externa.

Inclusion criteria included a longstanding, antibiotic resistant, aural discharge treated with conventional topical and systemic antibiotics, antifungal and anti-inflammatory therapy.

Randomization and blinding

Random numbers list was generated by the computer to be used for the allocation of the participants. Participants were grouped according to the site of the lesion into a unilateral group and bilateral group. Block randomization with a block size of two was used with 1:1 ratio of Honey group and Placebo group in both the unilateral group and the bilateral group. The allocation sequence was concealed from the researchers enrolling and assessing participants. The study was assessor blinded.

Participants were randomly allocated to the study group (Honey group) and the control group (Placebo group). Patients of the Honey group were treated by using undiluted pure honey produced by the ministry of agriculture. On the other hand, patients of the Placebo group were treated by undiluted glycerol produced by Gomhoria Company for chemical industries.

Neither the researcher allocating the participants nor the assessing person knew the decoding of the groups in its relation to the allocation sequence. Data were collected by a junior pain resident who was blinded to the study.

Procedures

For all patients, comprehensive information about the participants was collected, including age, gender, and medical history. Conventional ENT examinations were performed.

Before randomization, the same procedures were applied to both groups. At day 0, patients completed a symptoms chart given to them including the four symptoms: discomfort, itchiness, wetness, and smell; rating each of the first three symptoms according to severity as (no, mild, moderate or severe) and the smell as odourless, offensive or very offensive. Then, the attending physician completed a signs chart for erythema, ulceration, granulation and discharge quantity rated according to the severity as (no, mild, moderate or severe). After that, the ear was meticulously cleaned under the microscope after taking a bacteriological swab for microbiological assessment with suction, and digital otoscopic photography was taken. The taken swabs were sent to bacteriology labs of Banha and Helwan Universities hospitals according to the place of examination of the patients.

After randomization, patients of the study group were treated by 1 ml undiluted pure honey produced by the ministry of agriculture. The patients were given a sialastic applicator after explaining how to use it. Then, the dose prescribed was 1 ml three times per day in the affected ear. However, patients of the Placebo group were treated by undiluted glycerol produced by Gomhoria Company for chemical industries.

The treatment plan was for 14 days, and swabbing and bacteriological examination from external auditory canals were done at the end of the treatment period (14 days). Also, patients were questioned about adverse events and study compliance. The patients completed symptoms charts after the treatment period. Also, the signs chart were completed by the physician after the treatment period.

Bacteriological investigation

Each swab that was obtained from all patients have undergone a bacteriological examination:

First step: all ear swabs were cultured on broth fluid media for doing bacterial count: One ml of the fluid from each sample was cultured in nine ml of broth culture media. Then, ten-fold serial dilutions for the broth media were done.

After 24 hours incubation at 37 C, the plates of blood agar and agar media were examined, and bacterial colonies were counted. The rest of the broth culture was inoculated on bacteriological (agar, blood agar, and Macconkey) and mycological media (Sabourad's dextrose agar media). The results of the count were estimated for each one ml taken from each sample.

Outcome measures

The primary outcome measure was the number of organisms in tenfold diluted broth culture in both groups after the treatment period.

Secondary outcome measures were: improvement of symptoms and signs after the treatment period in both groups as well as the incidence of any adverse events in both groups.

Statistical analysis and sample size justification

Sample size calculation suggested that a minimum of 33 subjects per group is required to detect 6% difference in the number of organisms in tenfold diluted broth culture between groups (taking type I or α error of 5%, type II or β error of 10%). The 6% difference was based on a pilot study on 20 participants, ten in each group. We decided to include 50 patients per group to allow for dropouts.

All statistical tests were made using a significance level of 95%. SPSS software (Statistical Package for the Social Sciences, version 20.0, SSPS Inc, Chicago, IL, USA) was used for the statistical analyses. Data were summarized by mean & standard deviation or median & interquartile range in the numerical data according to their distribution and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were made using the student t-test and the non-parametric Mann-Whitney test. For comparing categorical data, Chi-square test was performed. The Exact test was used instead when the expected frequency is less than five. P-values less than 0.05 were considered as statistically significant.

RESULTS

All children (116 subjects) who came to the center with the presentation of persistent otitis externa were asked to participate in the study. Sixteen subjects refused to participate. Enrolled subjects (100) were randomized to the Honey group and the Placebo group, 50 in each group. None was excluded after randomization. The dispositions of these subjects are shown (Figure 1).

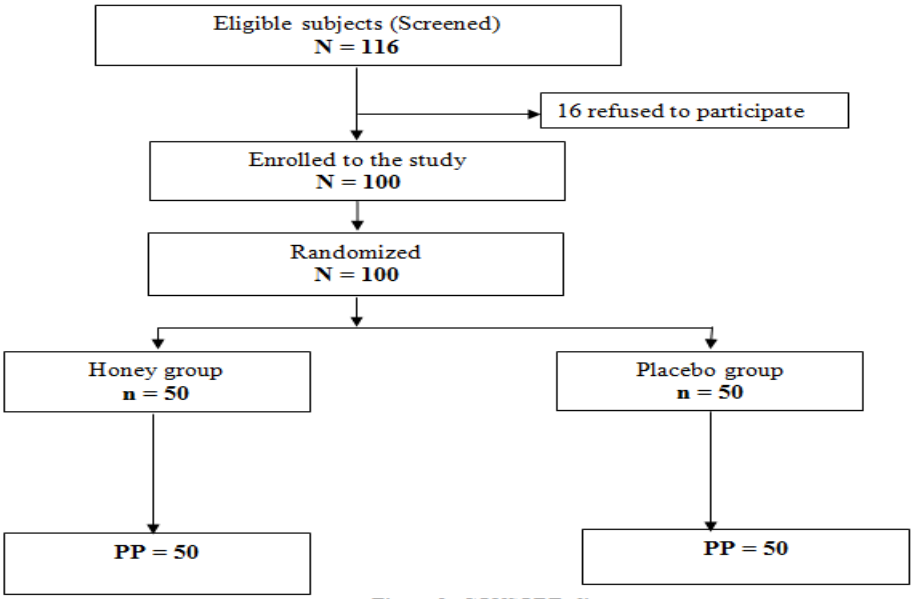

Figure 1: CONSORT diagram.

Baseline characteristics

A Hundred patients were included in the analysis, 50 in the Honey group and 50 in the Placebo group. There was no significant difference (p-value > 0.05) between the two groups regarding the age, gender, and side of the lesion. The median age was 29 (IQR = 19) years in the Honey group and 29 (20) years in the Placebo group (p-value 0.912). The majority of patients in both groups are males 58% & 64%, for the Honey group and the Placebo group, respectively (p-value = 0.539). The lesion was bilateral in 19 (38%) of the Honey group and 26 (52%) in the Placebo group, (p-value 0.159), as shown in Table 1.

Table 1: Baseline characteristics.

	Honey group	Placebo group	P-value
	N = 50	N = 50	
Gender, number (%)			
Male	29 (58%)	32 (64%)	
Female	21 (42%)	18 (36%)	0.539
Side, number (%)			
Bilateral	19 (38%)	26 (52%)	
Unilateral	31 (62%)	24 (48%)	0.159
Age in years,			
Median (interquartile range)	29 (19)	29 (20)	0.912
Mean (standard deviation)	28.95 (13.99)	29.98 (12.61)	

Assessment of the microbiology results before and after treatment

At the start of the study and before treatment, there was no significant difference in the number of organisms in tenfold diluted broth culture between groups (p-value 0.894) where it was 88.9(9.51) & 88.66 (8.34) in the Honey groups and the Placebo group, respectively. However, at the end of the study after two weeks of treatment, there was a significant difference in the number of organisms in tenfold diluted broth culture between groups (p-value < 0.001). It was 34.28(9.37) & 58.98 (11.44) in the Honey groups and the Placebo group, respectively (Table 2, Figures 2 & 3).

Some of the samples result in complete haemolysis on blood agar, and other samples lead to greenish discolorations or produce a foul smell or fishy odor. The types of the bacteria producing this colouration and smells need further bacteriological and mycological investigation.

Table 2: Microbiology results before and after treatment.

	Honey group N = 50	Placebo group N = 50	P-value
Before treatment	88.9 (9.51)	88.66 (8.34)	0.894
After treatment	34.28 (9.37)	58.98 (11.44)	< 0.001

Number of organisms in tenfold diluted broth culture.

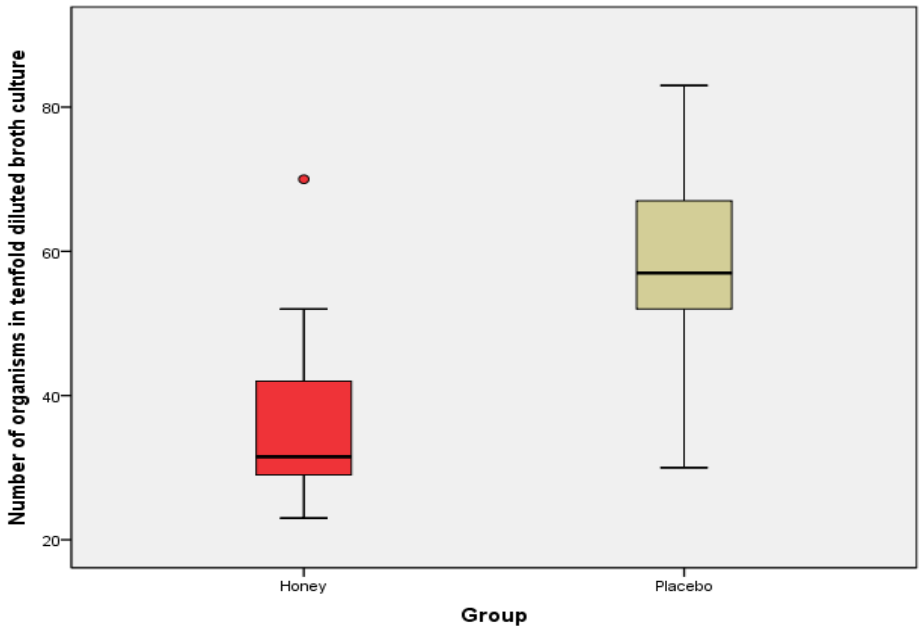

Figure 2: Microbiology results two weeks after treatment.

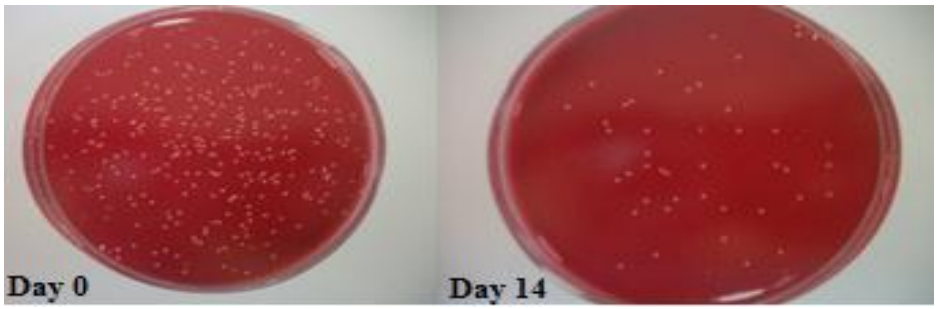

Figure 3: Microbiology results two weeks after treatment: Blood agar plates at day 0 and 14 in the Honey group.

Assessment of symptoms and signs before treatment and after 2-weeks follow-up

At the start of the study and before treatment, there was no significant difference in patient assessments of their symptoms (discomfort, itchiness, wetness, smell) between the Honey group and the Placebo group (p-values > 0.05).

However, at the end of the study and after two weeks of treatment, there was a very high significant difference in patient assessments of their symptoms (discomfort, itchiness, wetness, smell) between Honey group and the Placebo group (p-values < 0.001). Discomfort, itchiness, wetness and bad smell were improved significantly in the

Honey group more than in the Placebo group, as shown in Table 3.

Also, at the start of the study and before treatment, there was no significant difference in physician assessments of the signs of otitis externa (erythema, ulceration, granulation and discharge quantity) between the Honey group and the Placebo group (p-values > 0.05). However, at the end of the study and after two weeks of treatment, there was a very high significant difference in physician assessments of the signs of otitis externa between Honey group and the Placebo group (p-values < 0.001). Erythema, ulceration, granulation, and discharge quantity were improved significantly in the Honey group more than in the Placebo group, as shown in Table 3. During the study period, there were no adverse events for the Honey drops, as shown in Table 4.

Table 3: Symptoms before and after treatment.

	Baseline			After intervention		
	Honey n (%)	Placebo n (%)	p-value	Honey n (%)	Placebo n (%)	p-value
Discomfort						
No	0 (0)	0 (0)	0.564	22 (44)	0 (0)	< 0.001
Mild	0 (0)	0 (0)		26 (52)	0 (0)	
Moderate	6 (12)	8 (16)		2 (4)	6 (12)	
Severe	44 (88)	42 (84)		0 (0)	44 (88)	
Itchiness						
No	0 (0)	0 (0)	0.603	21 (42)	0 (0)	< 0.001
Mild	0 (0)	0 (0)		27 (54)	0 (0)	
Moderate	8 (16)	10 (20)		2 (4)	6 (12)	
Severe	42 (84)	40 (80)		0 (0)	44 (88)	
Wetness						
No	0 (0)	0 (0)	0.585	21 (42)	0 (0)	< 0.001
Mild	0 (0)	0 (0)		27 (54)	0 (0)	
Moderate	7 (14)	9 (18)		2 (4)	4 (8)	
Severe	43 (86)	41 (82)		0 (0)	46 (92)	
Smell						
Odourless	0 (0)	0 (0)	0.661	48 (96)	0 (0)	< 0.001
Offensive	47 (94)	47 (94)		2 (4)	12 (24)	
Very offensive	3 (6)	3 (6)		0 (0)	38 (76)	

Table 4: Signs before and after treatment.

	Baseline			After intervention		
	Honey n (%)	Placebo n (%)	p-value	Honey n (%)	Placebo n (%)	p-value
Erythema						
No	0 (0)	0 (0)	0.727	22 (44)	0 (0)	< 0.001
Mild	0 (0)	0 (0)		26 (52)	0 (0)	
Moderate	5 (10)	4 (8)		2 (4)	6 (12)	
Severe	45 (90)	46 (92)		0 (0)	44 (88)	
Ulceration						
No	45 (90)	39 (78)	0.241	22 (44)	0 (0)	< 0.001
Mild	2 (4)	2 (4)		26 (52)	0 (0)	
Moderate	2 (4)	3 (6)		2 (4)	4 (8)	
Severe	1 (2)	6 (12)		0 (0)	46 (92)	
Granulation						
No	34 (68)	32 (64)	0.461	22 (44)	0 (0)	< 0.001
Mild	0 (0)	1 (2)		26 (52)	0 (0)	
Moderate	11 (22)	13 (26)		2 (4)	4 (8)	
Severe	5 (10)	4 (8)		0 (0)	46 (92)	
Discharge quantity						
No	0 (0)	0 (0)	0.695	22 (44)	0 (0)	< 0.001
Mild	0 (0)	0 (0)		26 (52)	0 (0)	
Moderate	3 (6)	4 (8)		2 (4)	4 (8)	
Severe	47 (94)	46 (92)		0 (0)	46 (92)	

DISCUSSION

This randomized placebo-controlled trial was conducted to compare the efficacy and safety of Honey ear drops versus placebo drops in cases of persistent chronic otitis externa. The results if our study showed that Honey has clinical and bacteriological efficacy as well as it demonstrated an excellent safety profile. At the end of our study, the number of organisms in tenfold diluted broth culture was significantly lower in the Honey groups than in the Placebo group.

Moreover, at the end of the study, improvement of patients' symptoms (discomfort, itchiness, wetness, and smell) was significantly higher in the Honey group than in the Placebo group. Also, at the end of the study, improvement of signs of chronic otitis externa (erythema, ulceration, granulation and discharge quantity) was significantly higher in the Honey group than in the Placebo group.

It worth saying that some of the samples results in complete haemolysis on blood agar, and other samples results in greenish discolorations or produce foul smell or fishy odor. The types of the bacteria producing these colouration and smells need further bacteriological and mycological investigation.

As far as we know, the only study that addressed the use of honey for otitis externa in human was that of Henatsch et al. (2017).[8] It was a proof-of-concept study for the treatment of the recurrent eczematous otitis externa in a prospective case series. The authors investigated the clinical effect and the in-vitro antibacterial potential of medical honey eardrops. They recruited fifteen patients with recurrent eczematous external otitis and treated them with eardrops of medical honey for two weeks. The results of their study were in accordance to our study as it showed that treatment with honey resulted in less discomfort and itchiness and decreased signs of eczema without adverse events. Besides, honey showed a potent in-vitro inhibitory activity against several tested strains; however, it did not eradicate the infection with Staphylococcus aureus in vivo.[8]

In addition to its high nutritional value, honey has been shown to have promising properties of being anti-microbial, anti-inflammatory, antioxidant agent as well as an anti-tussive and wound healing features. Besides, honey improves the concentration of serum testosterone, increases the sperm count, and enhances fertility.[10]

Extensive research studies have been done to investigate the bioactive compounds of honey. The presence of such active compounds provides a better understanding of the possible biological role of honey.[10]

Researchers depicted that honey has various essential bioactive compounds. These include vitamins (A, E, K, B1, B2, B6, Niacin, Vitamin C, Pantothenic acid and phenolics, fatty acids, and flavonoids).[11,14] In addition, it contains acacetin, abscisic acid, apigenin, pinocembrin, ferulic acid, and several amino acids like arginine, cysteine, glutamic acid, aspartic acid, and proline.[15,17]

Moreover, the literature suggested that honey has many potent antioxidative agents. Therefore, honey has numerous pre-emptive characteristics against inflammatory disorders, neurological worsening, coronary artery diseases, cancer and aging process. Increase in the phenolic compound in honey provides antioxidant property.[11,18,20]

Not only honey is antioxidant, but also it has antimicrobial activities as it has low pH and high osmolarity combined to the hydrogen peroxide.[21] Also, the antibacterial activity of honey is not only reliant on its peroxide activity but also on other non-peroxide mechanisms.[22] Nowadays, there is growing evidence that honey has a broad spectrum activity against both gram-positive and gram-negative bacteria.[23] In addition, some honey kinds exhibit a broad-spectrum antimicrobial role against antibiotic-resistant bacterial pathogens.[24,27] The differences in the profile of anti-microbial activity regarding type and level are dependent on the varieties of the floral sources for the honey.[28]

Despite the advantages of this study being randomized controlled trial with enough sample size and objective measurements, it has some weak points like it has no long-term follow up of the adverse events and it did not determine the causative organisms.

CONCLUSIONS

In conclusion, Honey is effective and safe as an ear drops for cases having persistent chronic otitis externa. Further studies are recommended to study its effect on different causative organisms.

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